CARDIAC EMBRYOLOGY
EARLY DEVELOPMENT OF HEART

Dr.Santhosh Narayanan

- FORMATION OF TRILAMINAR EMBRYO
- CARDIOGENESIS
- MOLECULAR DEVELOPMENT OF HEART
- DEVELOPMENTAL ABNORMALITIES

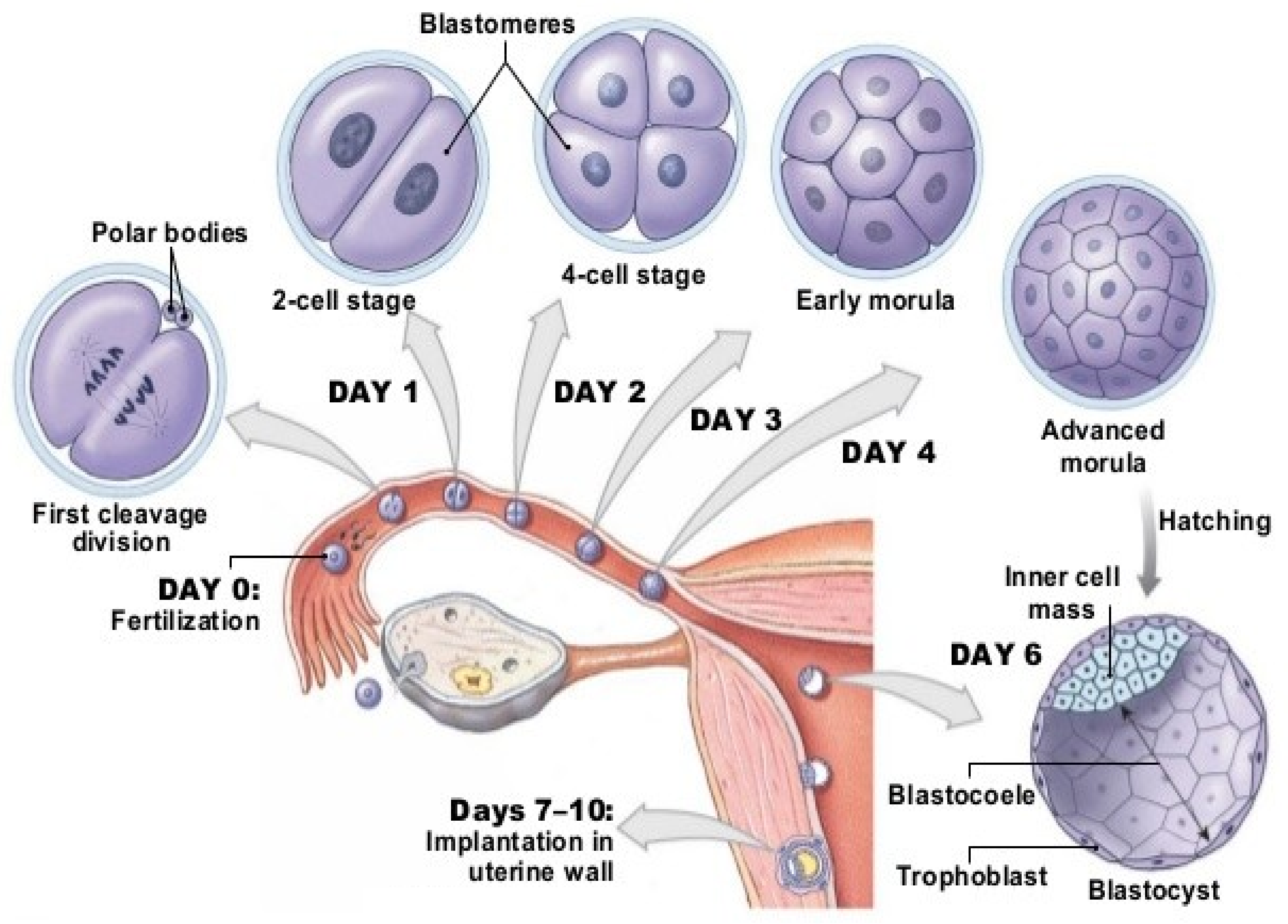
The Beginning

DAY 0 - FERTILISATION

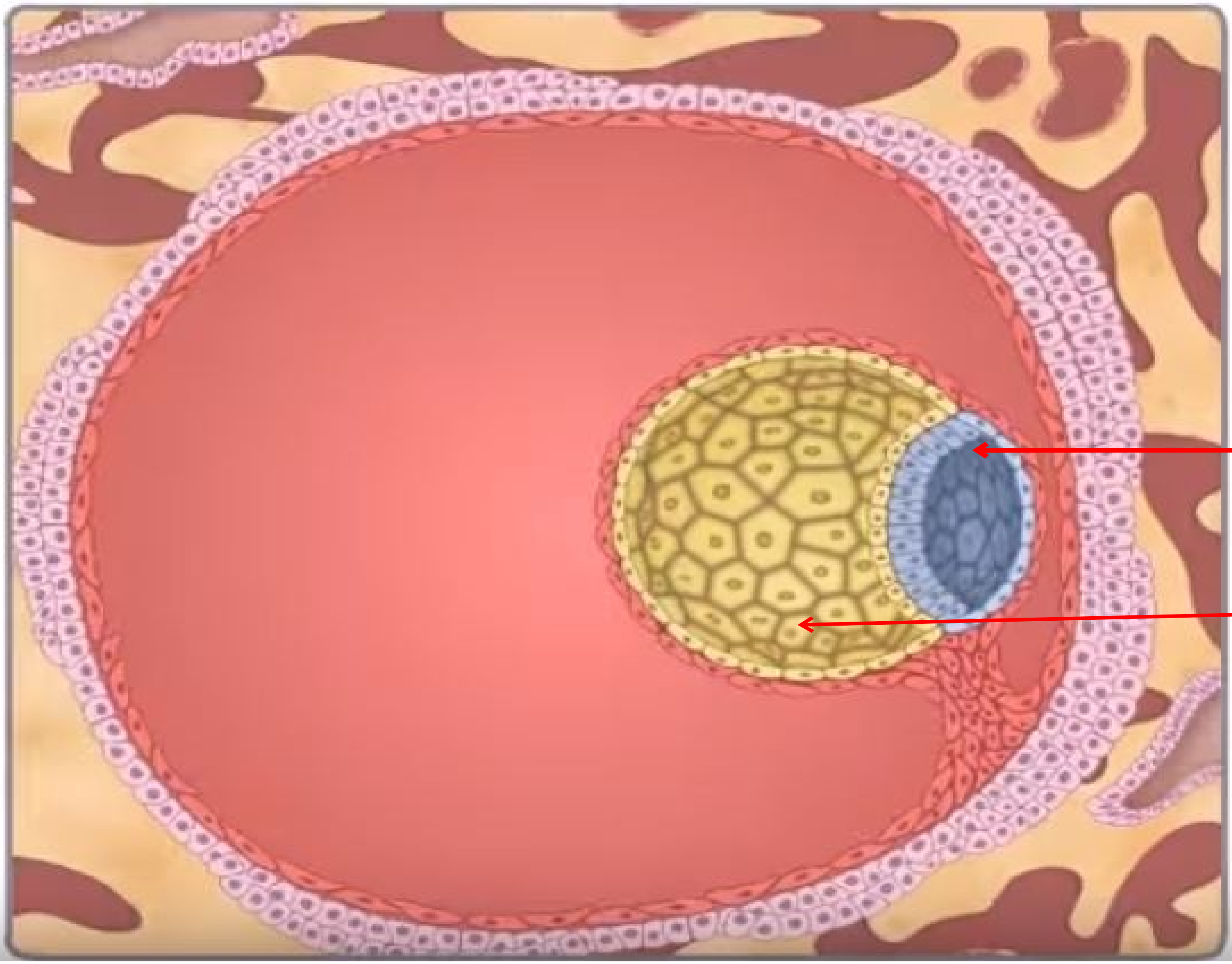
DAY 1 -4 - CELL DIVISION- MORULA

DAY 5-6 - BLASTOCYST

DAY 7-10 - IMPLANTATION


Blastomeres
Polar bodies
2-cell stage
4-cell stage
Early morula
Advanced morula
First cleavage division
DAY 1
DAY 2
DAY 3
DAY 4
Hatching
DAY 0:
Fertilization
Inner cell mass
DAY 6
Blastocoele
Days 7–10:
Implantation in uterine wall
Trophoblast
Blastocyst

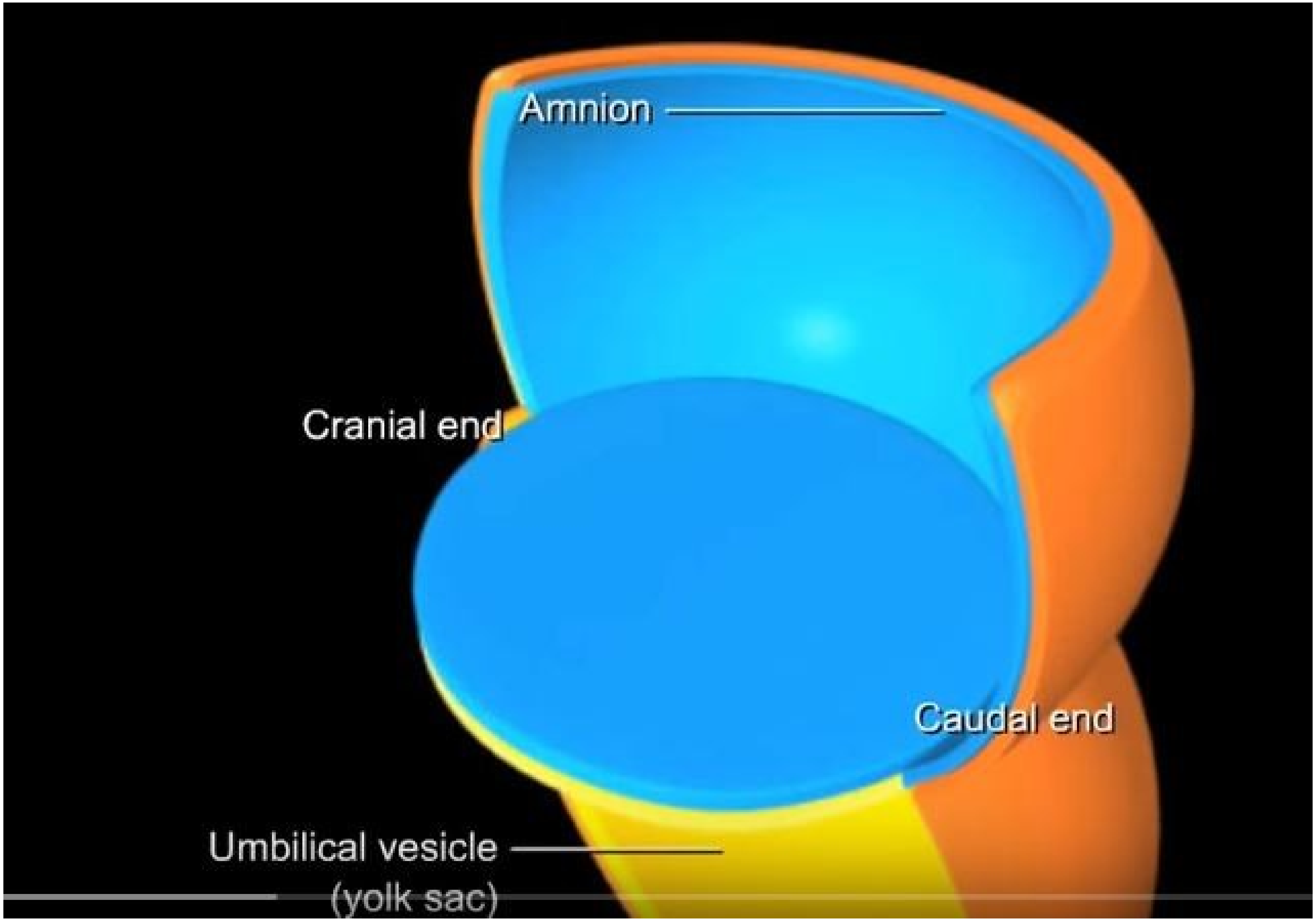
Bilaminar embryo (Days 11-14)



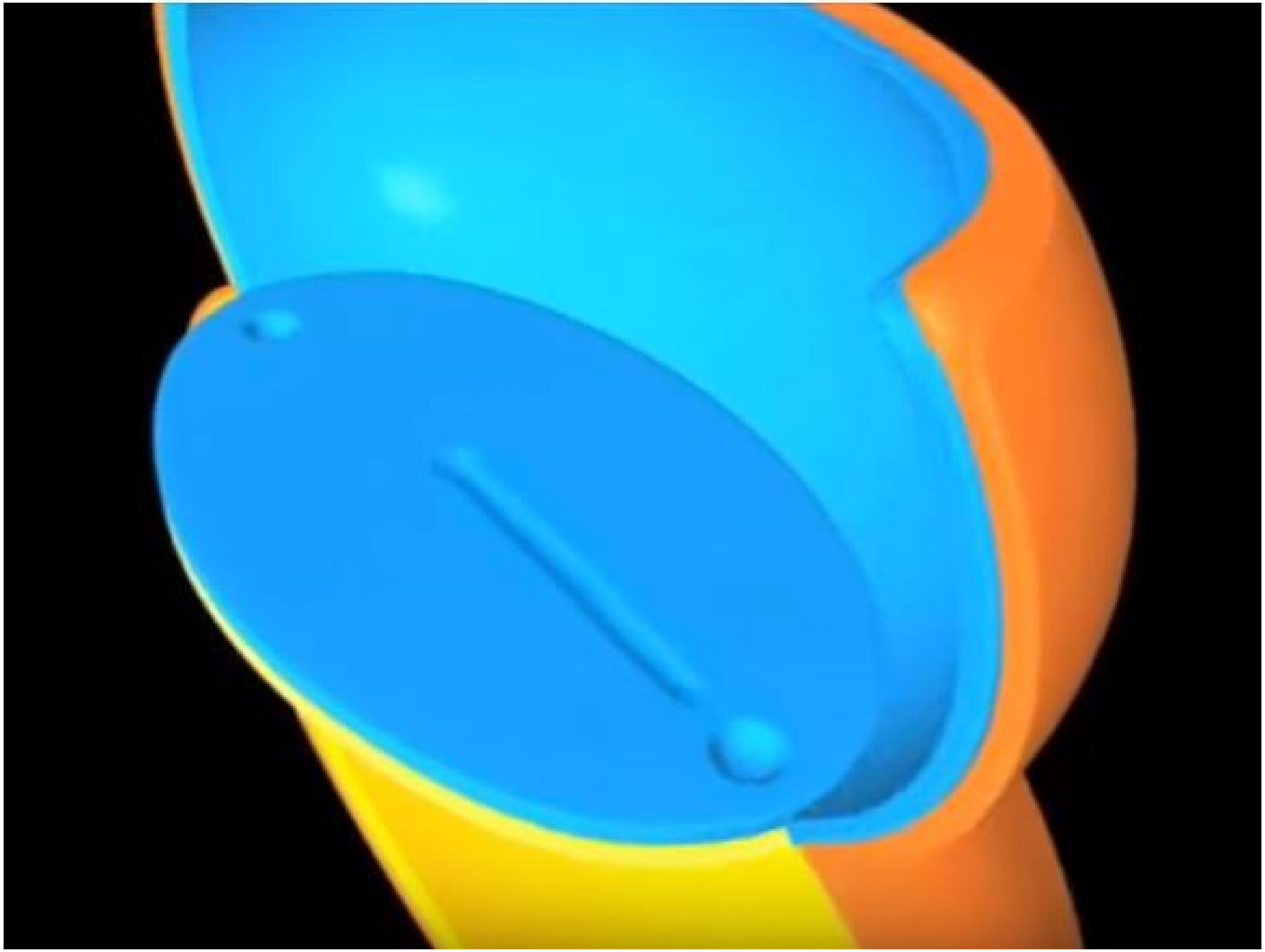
EPIBLAST

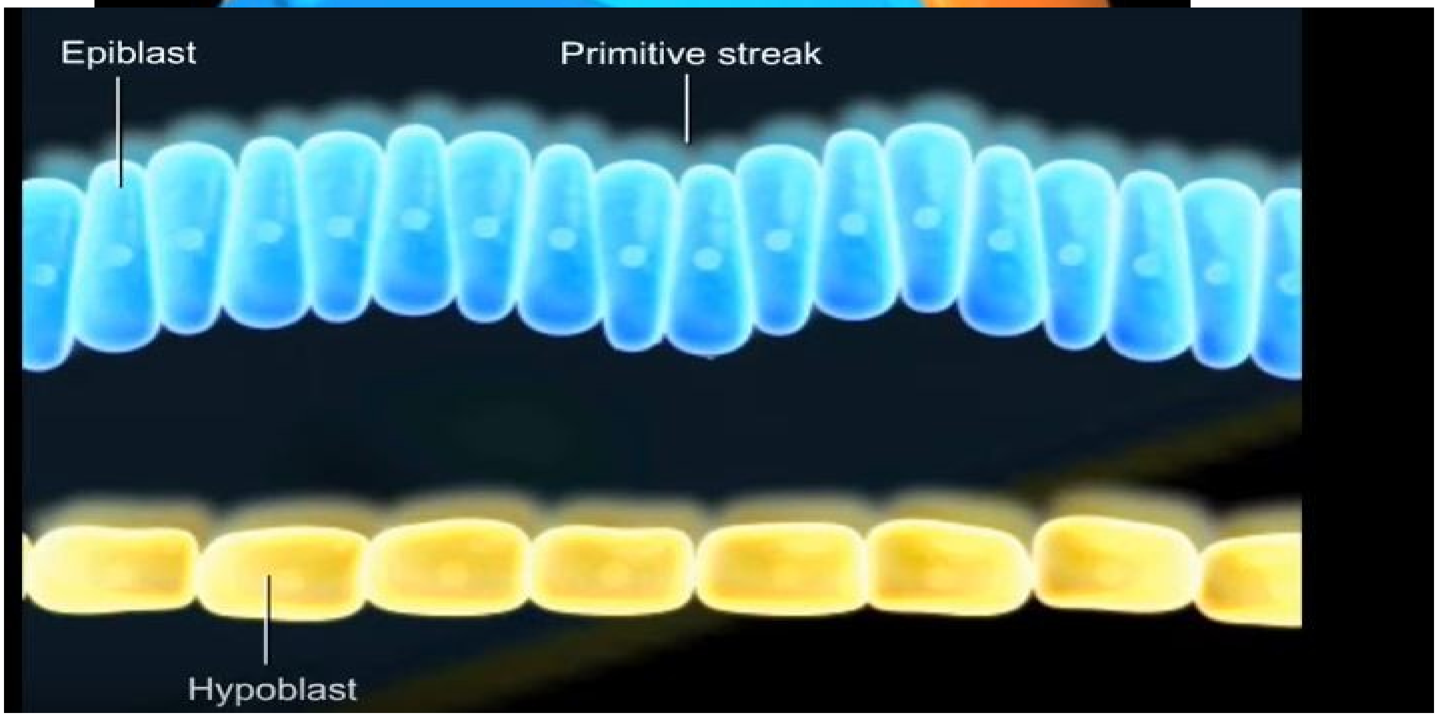
HYPOBLA
ST

The Amnion and Yolk sac

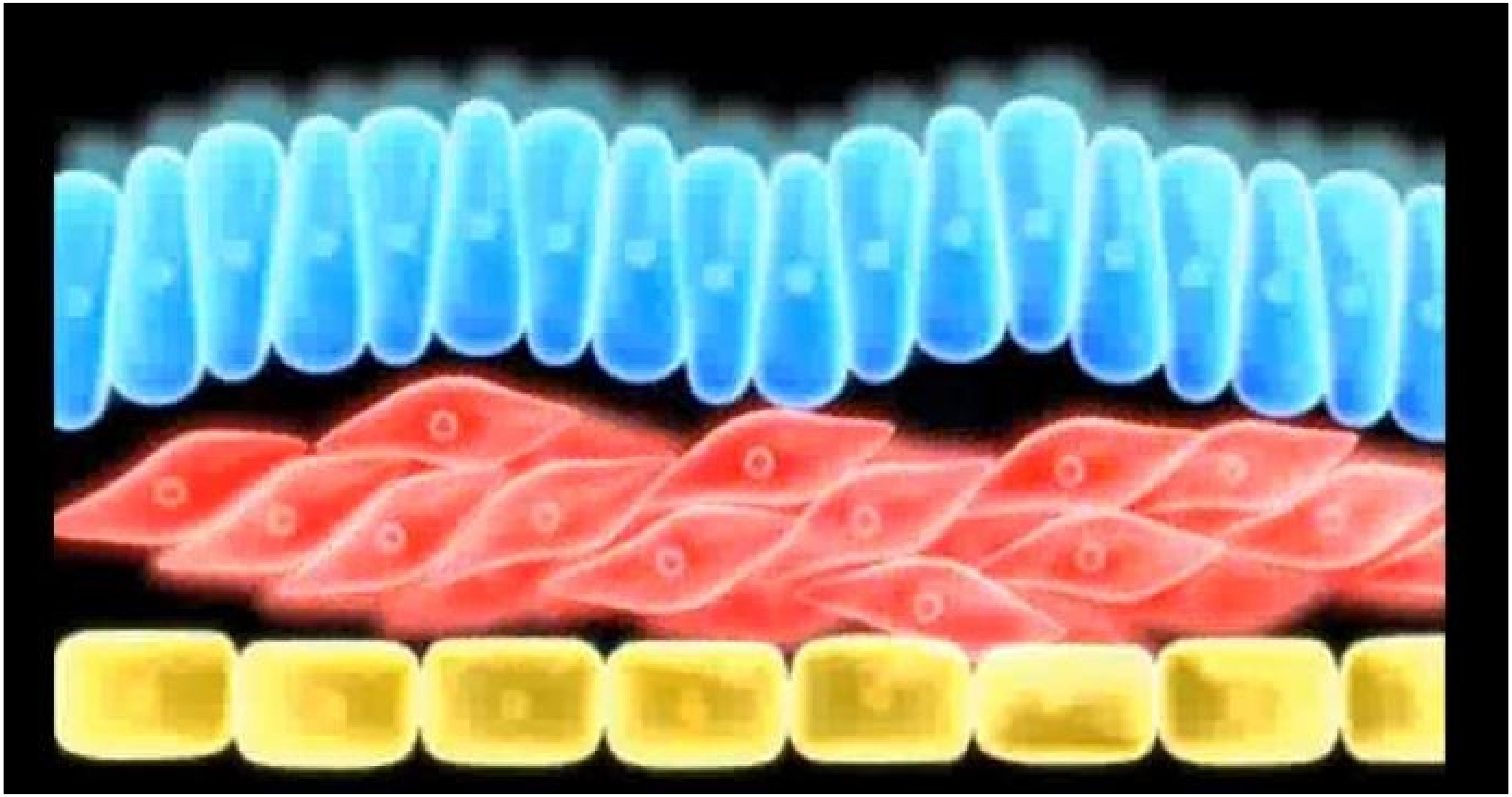


Primitive streak week 3

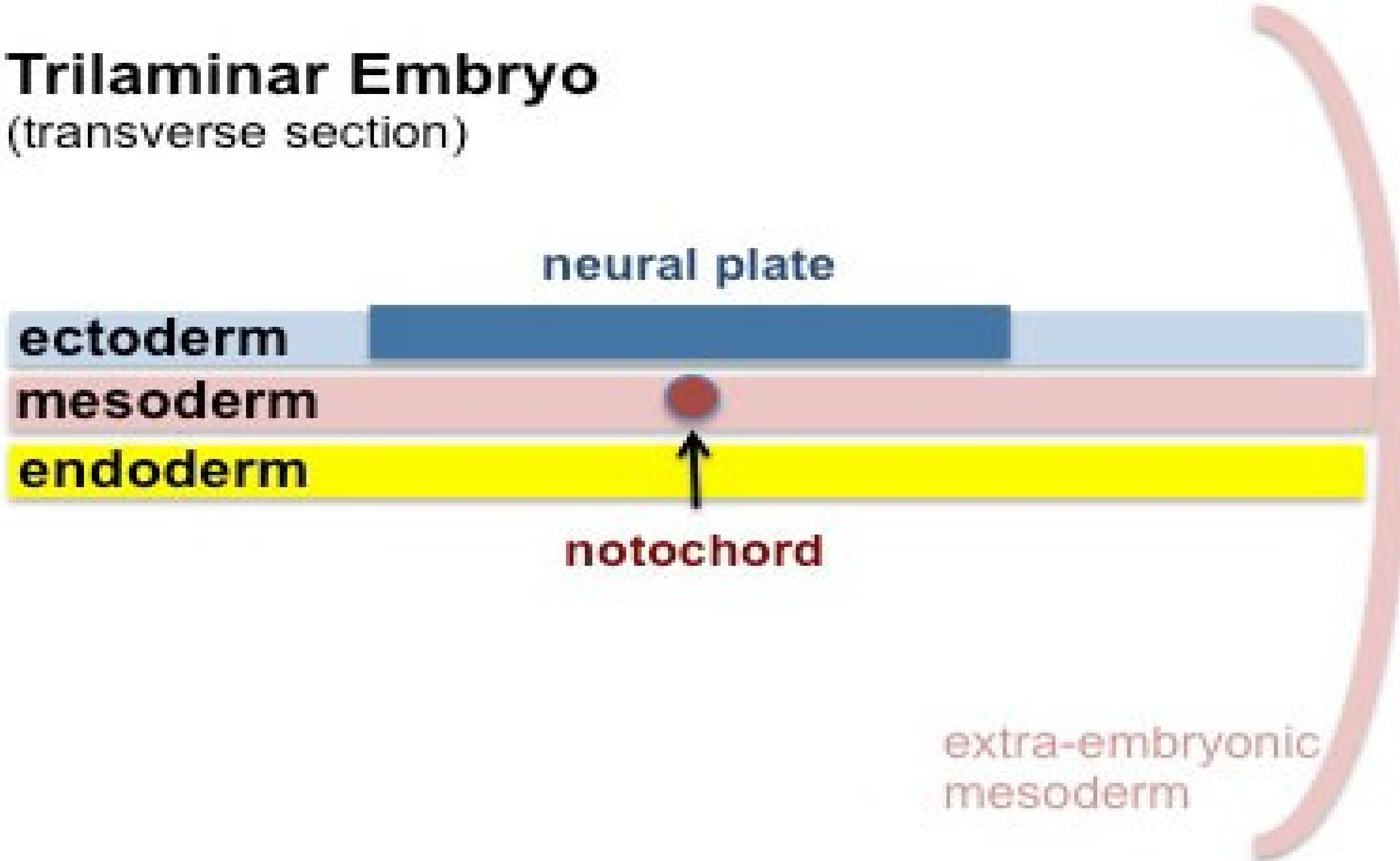



Epiblast
Primitive streak
Hypoblast

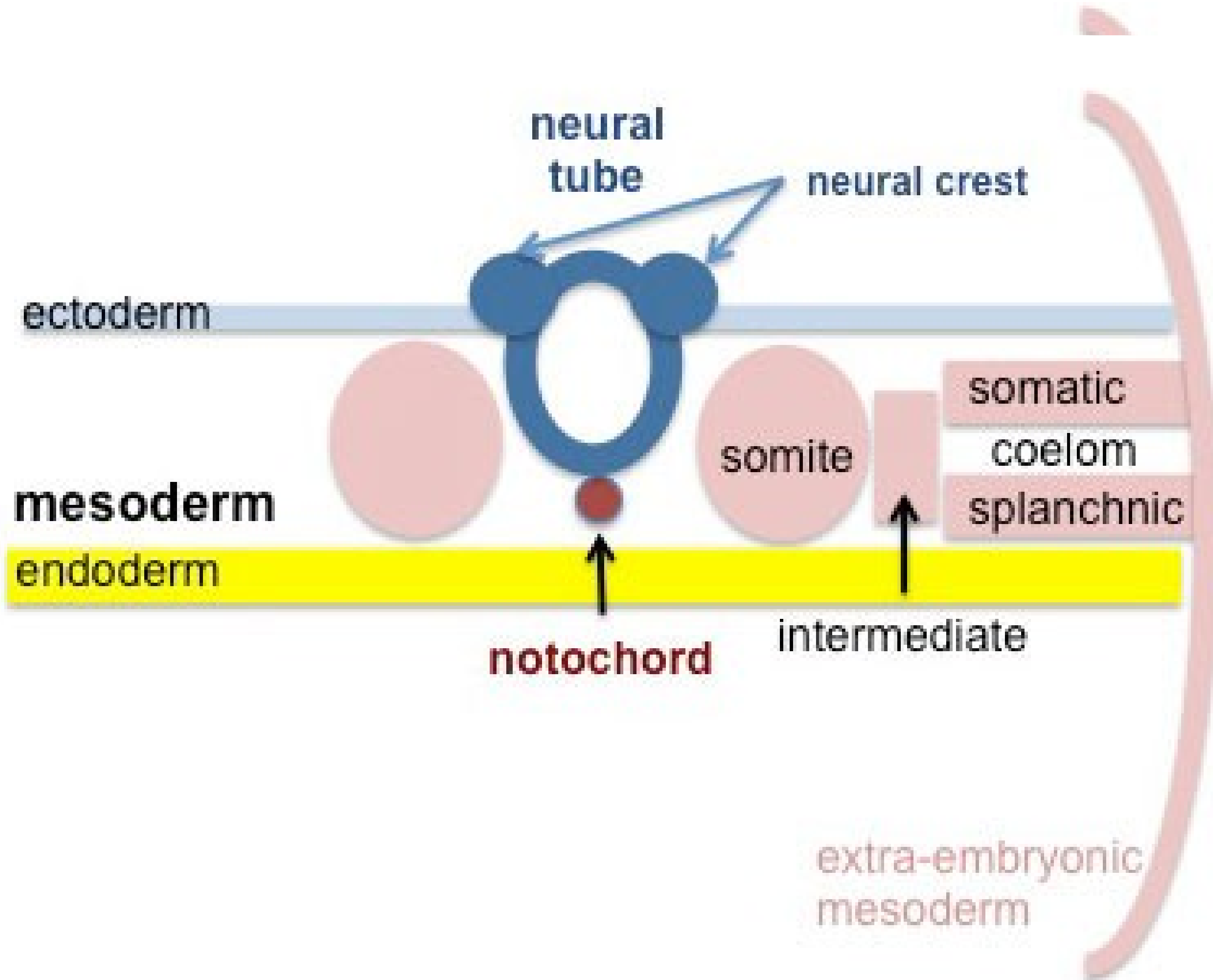
Gastrulation - Week 3



Neurulation



Neurulation



Derivatives of Germ layers

ECTODERM	MESODERM	ENDODERM
• Epidermis of skin and its derivatives (including sweat glands, hair follicles) • Epithelial lining of mouth and anus • Cornea and lens of eye • Nervous system • Sensory receptors in epidermis • Adrenal medulla • Tooth enamel • Epithelium of pineal and pituitary glands	• Notochord • Skeletal system • Muscular system • Muscular layer of stomach and intestine • Excretory system • Circulatory and lymphatic systems • Reproductive system (except germ cells) • Dermis of skin • Lining of body cavity • Adrenal cortex	• Epithelial lining of digestive tract • Epithelial lining of respiratory system • Lining of urethra, urinary bladder, and reproductive system • Liver • Pancreas • Thymus • Thyroid and parathyroid glands

The Cardiogenesis

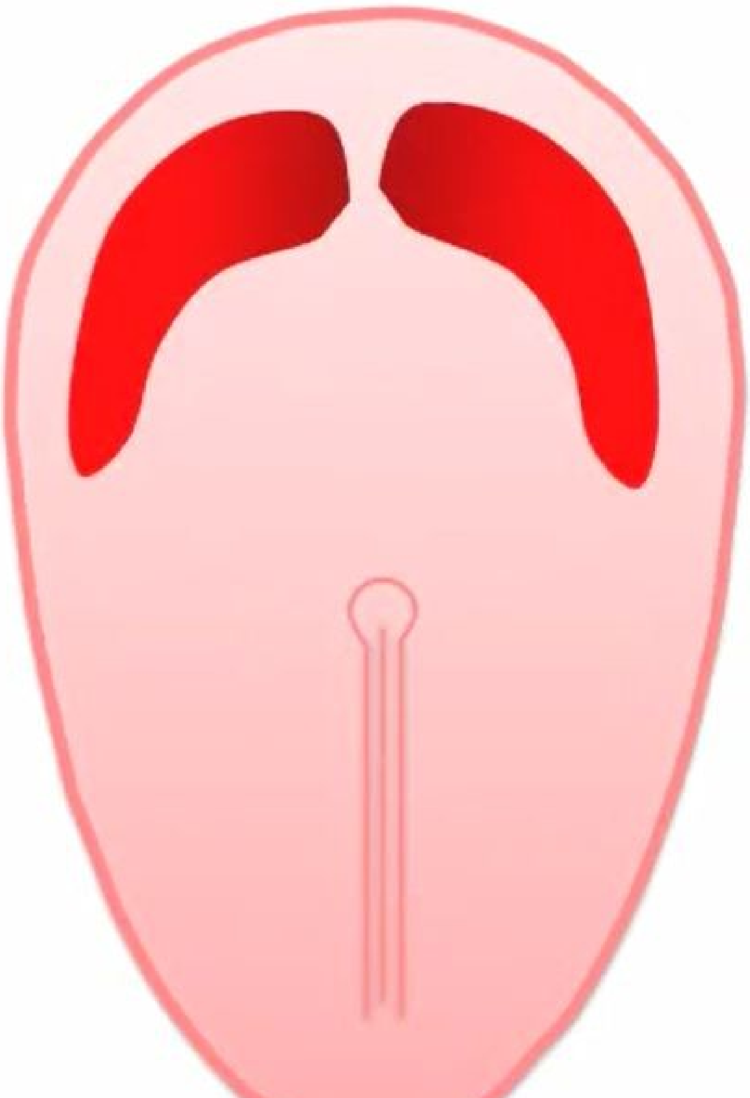
CARDIOGENESIS

- Formation of bilateral heart fields
- Formation of the heart tube

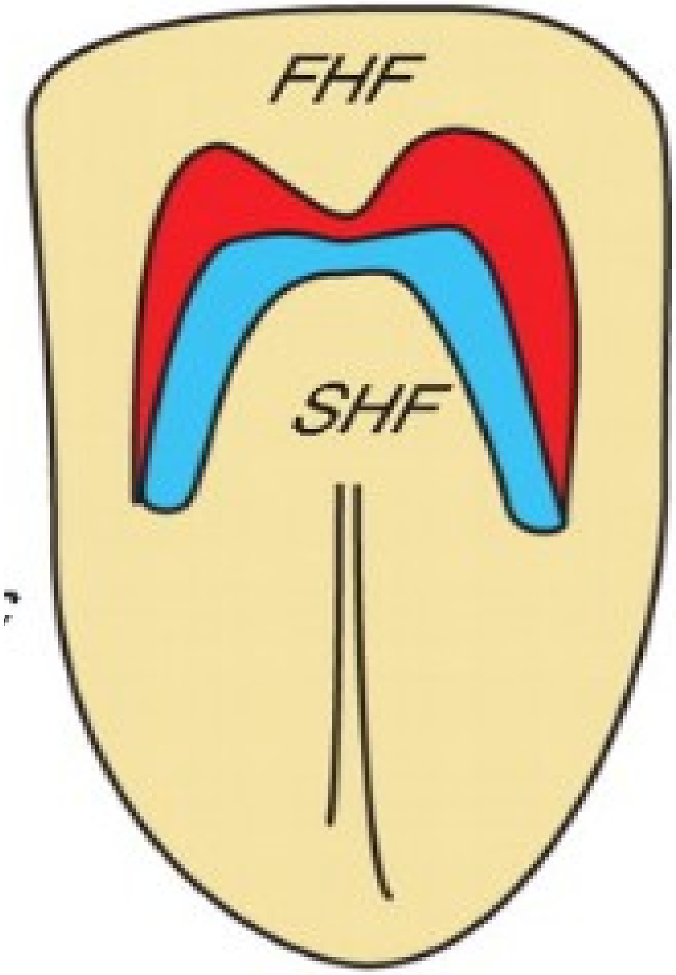
- Folding of the heart tube
- Looping of the heart tube
- Chamber specification and compaction

Cardiac precursor cells

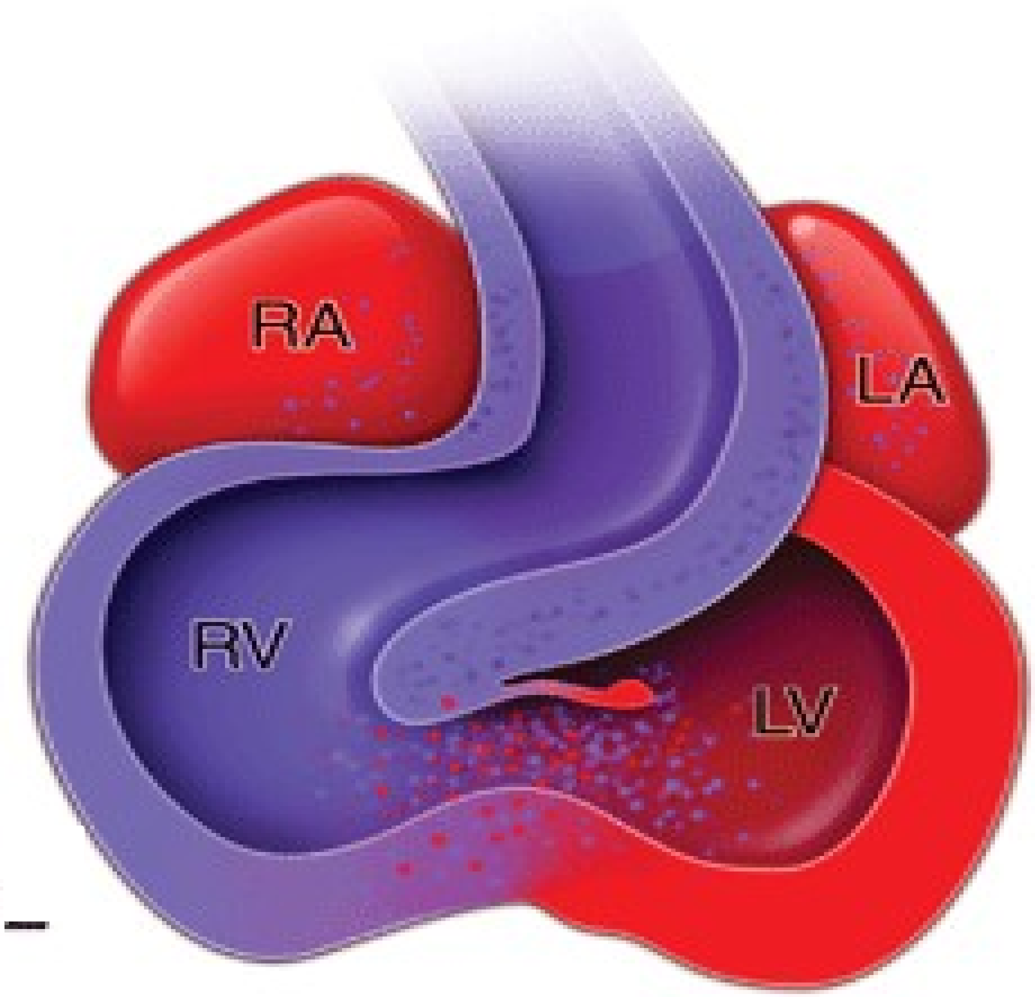
- First heart field
- Second heart field
- Neural crest cells
- Pro epicardium

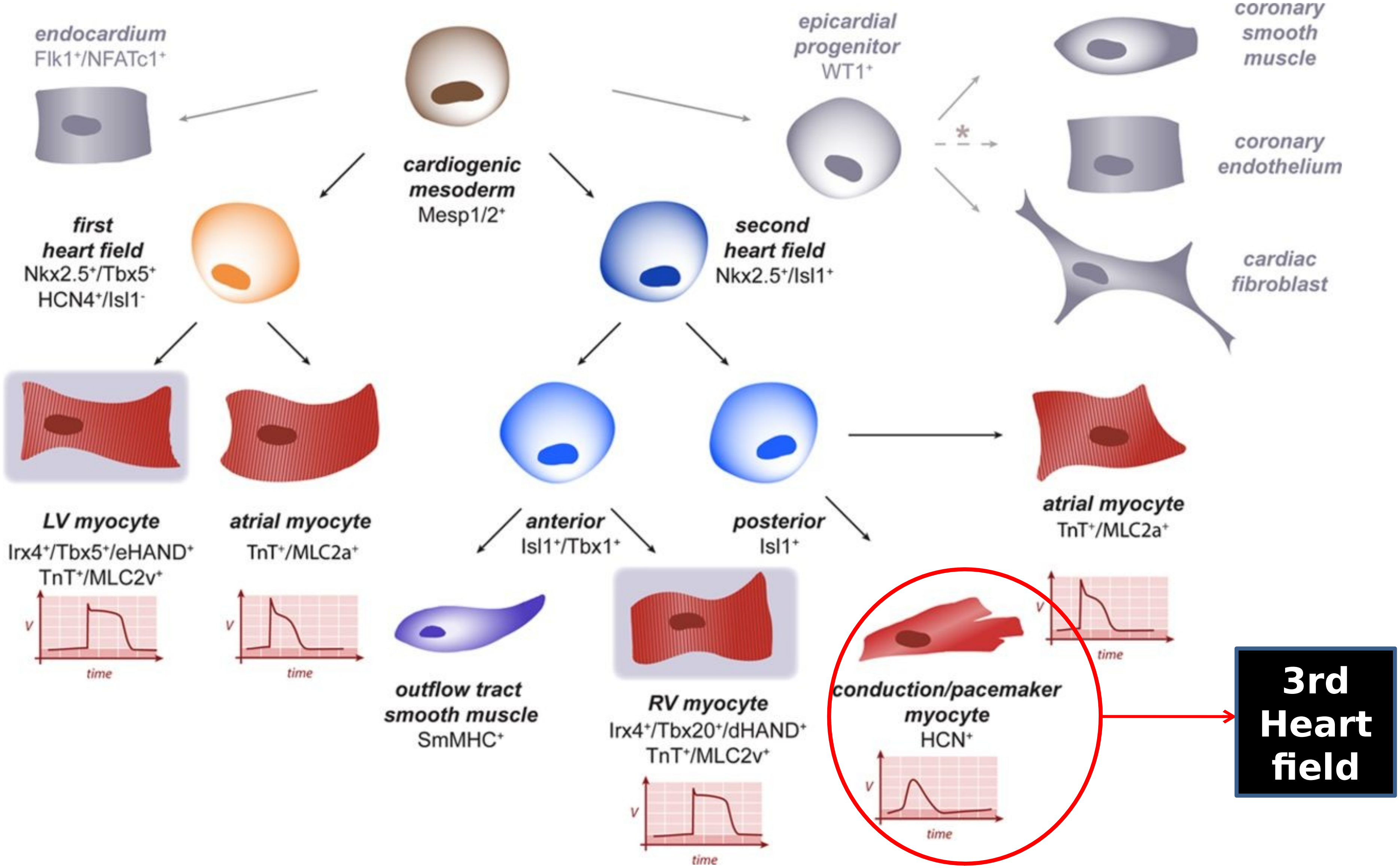


The "Cardiac Crescent"



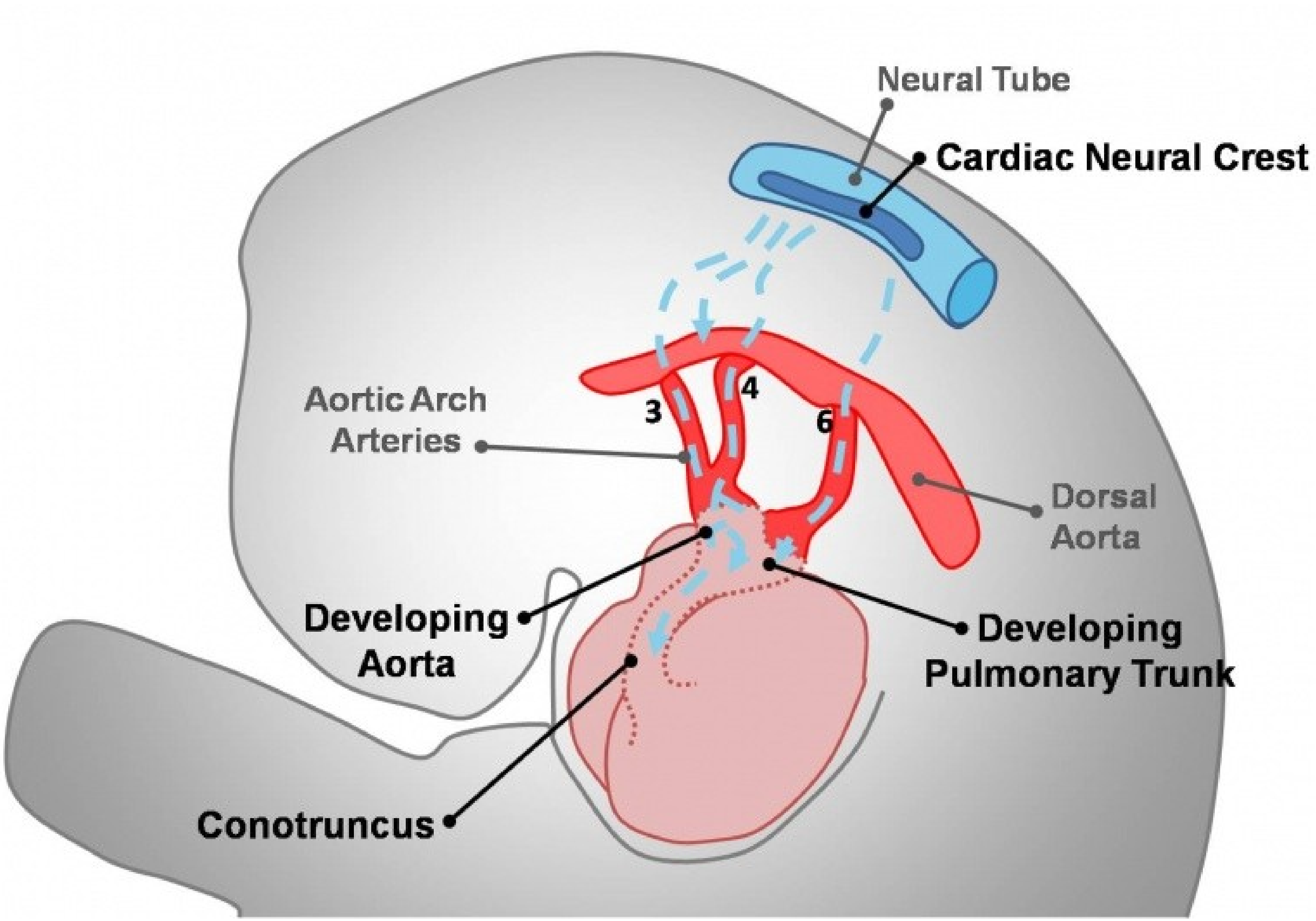
The second heart field





endocardium
Flk1+/NFATc1+
cardiogenic
mesoderm
Mesp1/2+
epicardial
progenitor
WT1+
coronary
smooth
muscle
*
coronary
endothelium
cardiac
fibroblast
first
heart field
Nkx2.5+/Tbx5+
HCN4+/Isl1-
second
heart field
Nkx2.5+/Isl1+
LV myocyte
Irx4+/Tbx5+/eHAND+
TnT+/MLC2v+
V
time
atrial myocyte
TnT+/MLC2a+
V
time
anterior
Isl1+/Tbx1+
posterior
Isl1+
atrial myocyte
TnT+/MLC2a+
V
time
outflow tract
smooth muscle
SmMHC+
RV myocyte
Irx4+/Tbx20+/dHAND+
TnT+/MLC2v+
V
time
conduction/pacemaker
myocyte
HCN+
V
time
3rd
Heart
field

The Cardiac Neural crest



Sequence of Events

- **<u>Day I8</u>** - Cardiac precursor cells seen in the form of blood islands

- **<u>Day 20</u>** - First intraembryonic blood vessels

- **<u>Day 21</u>**- Folding, heart tube formation,looping
- **<u>Day 22</u>** – heart starts to beat
- **<u>Day 28</u>** – embryonic circulation

Folding of Embryo

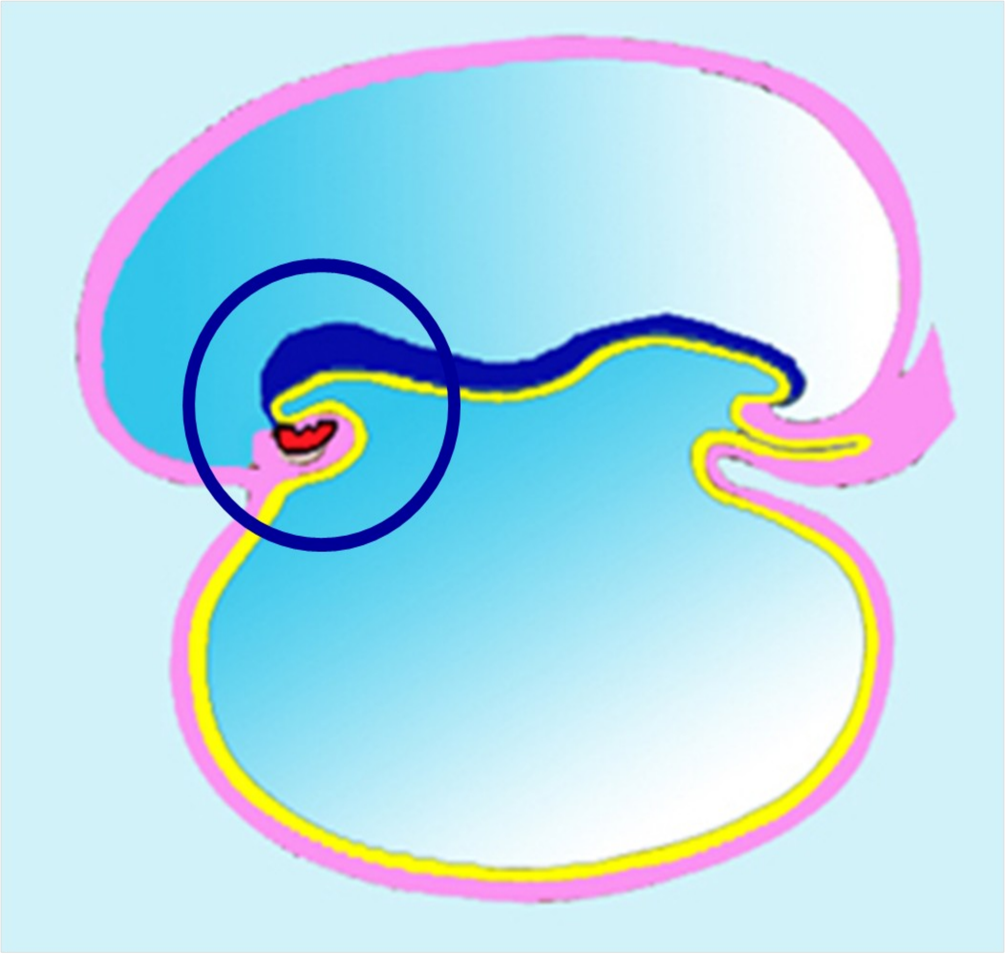
CRANIOCAUDAL AXIS

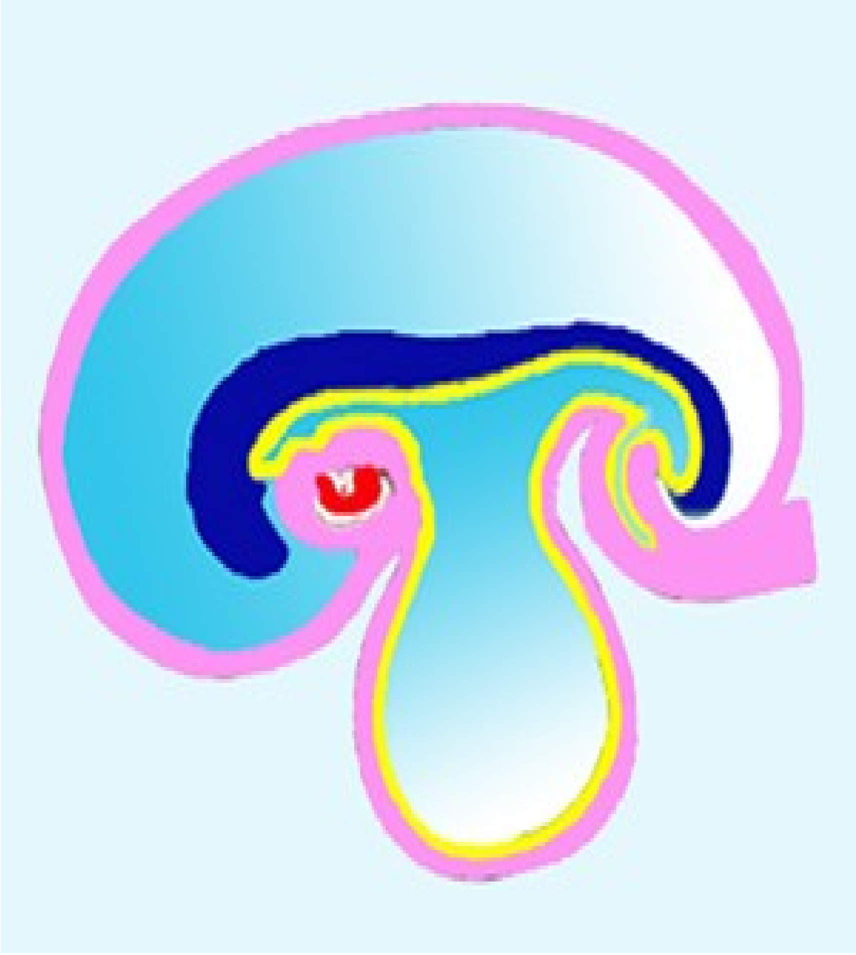
- More rapid growth of the neural tube forming the brain at its cephalic end.
- Growth in this direction will cause the embryo to become convex shaped.

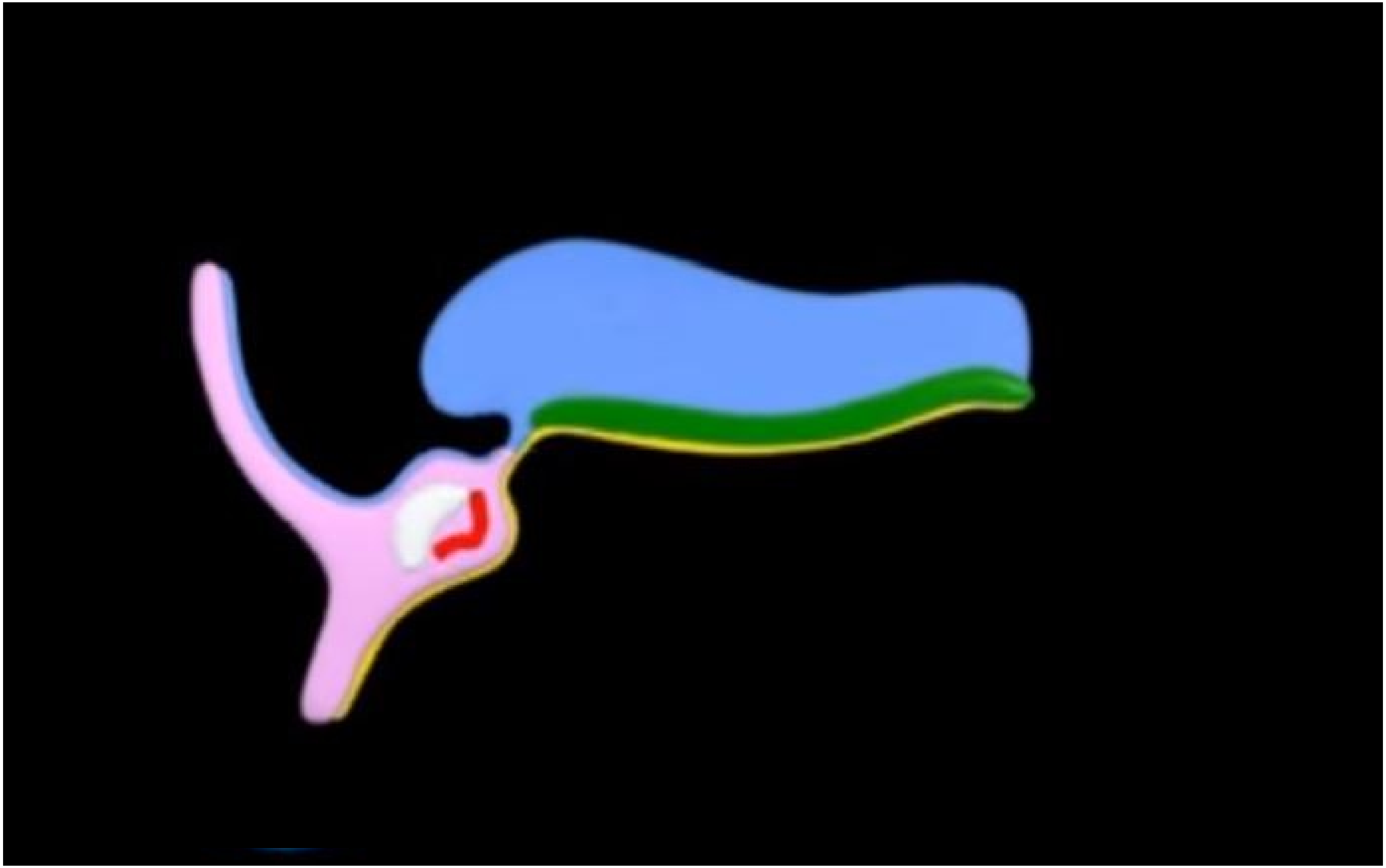
LATERAL FOLDING

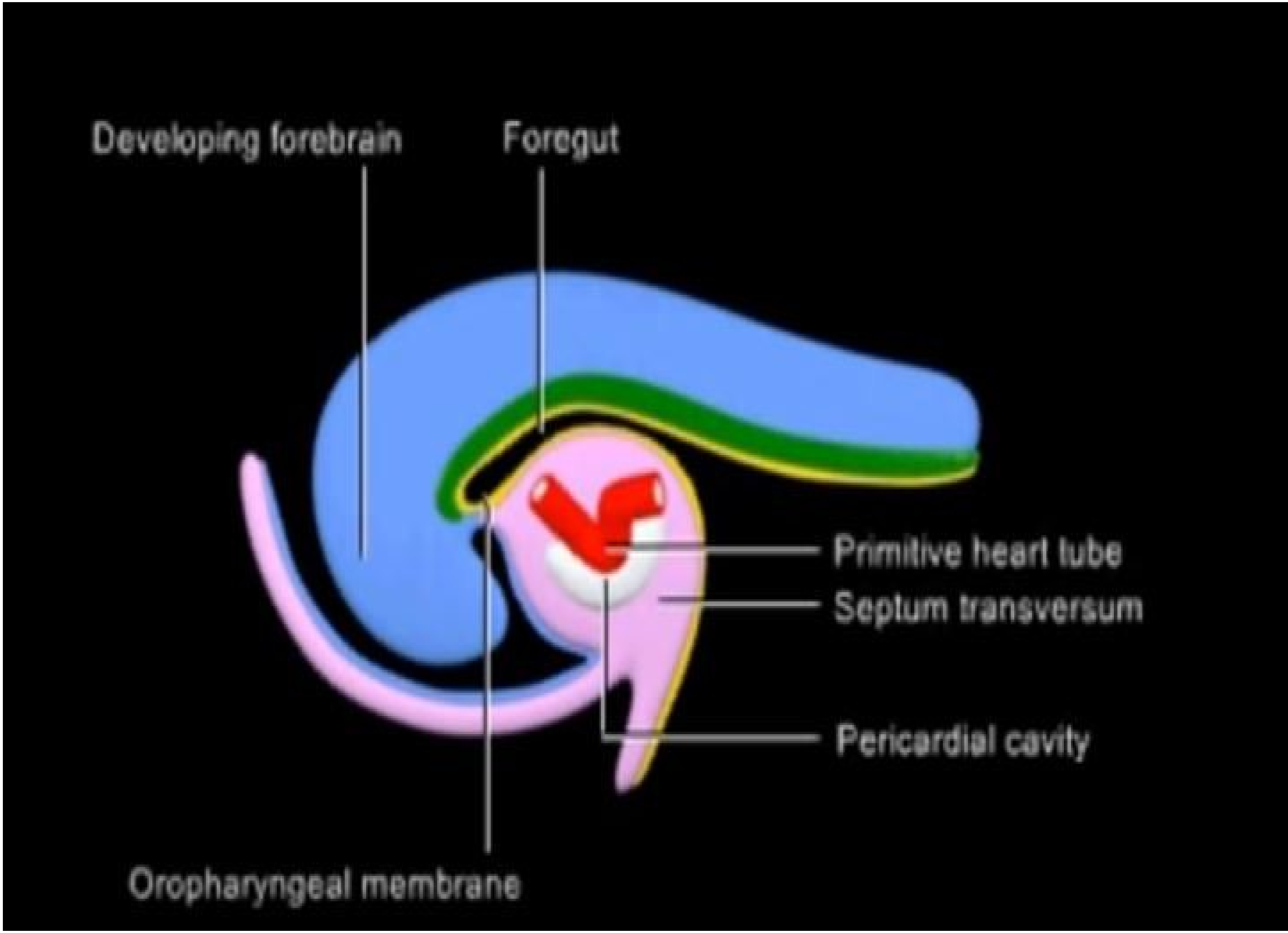
Two lateral edges of the germ disk fold forming a tube-like structure

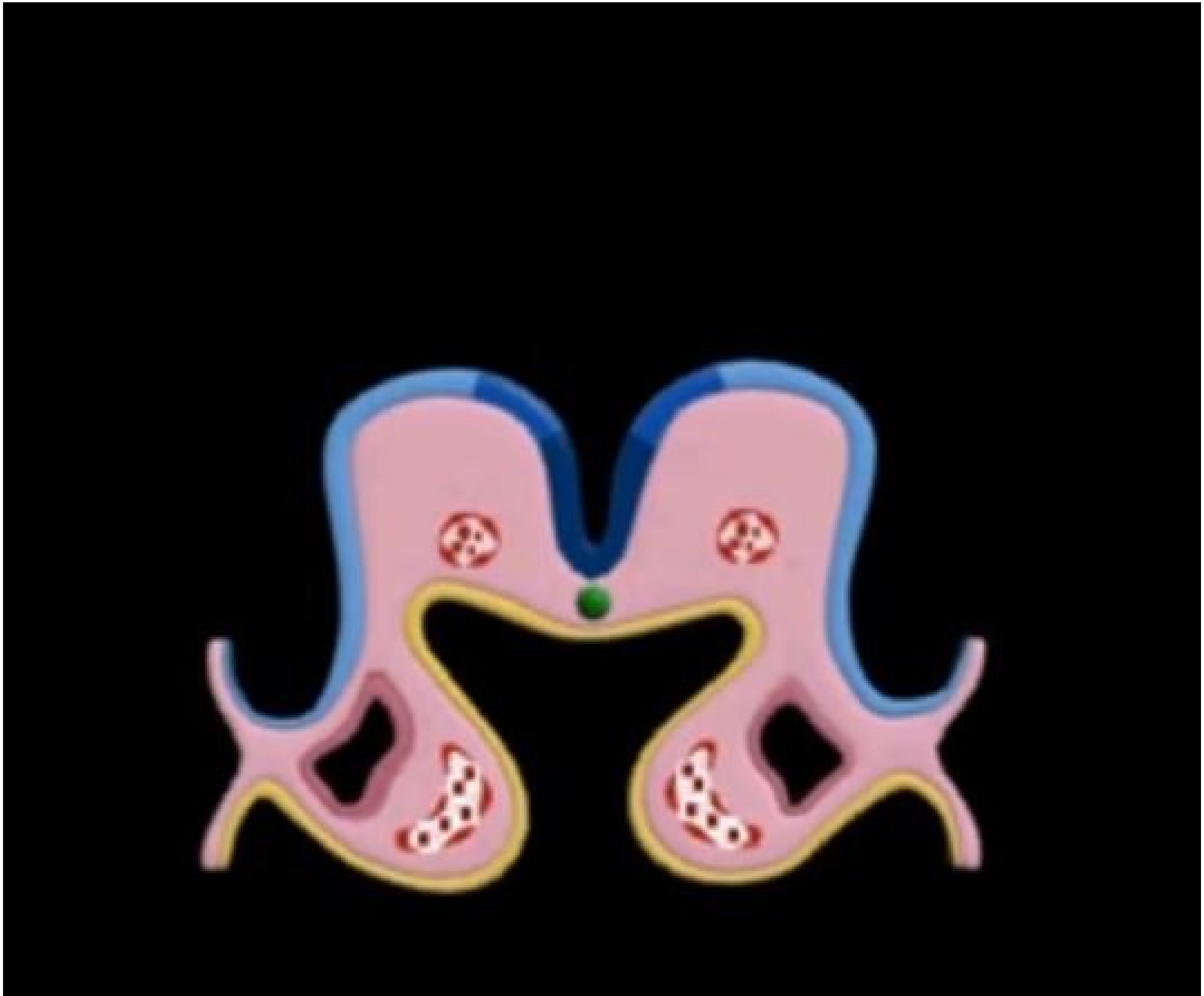
Folding of embryo

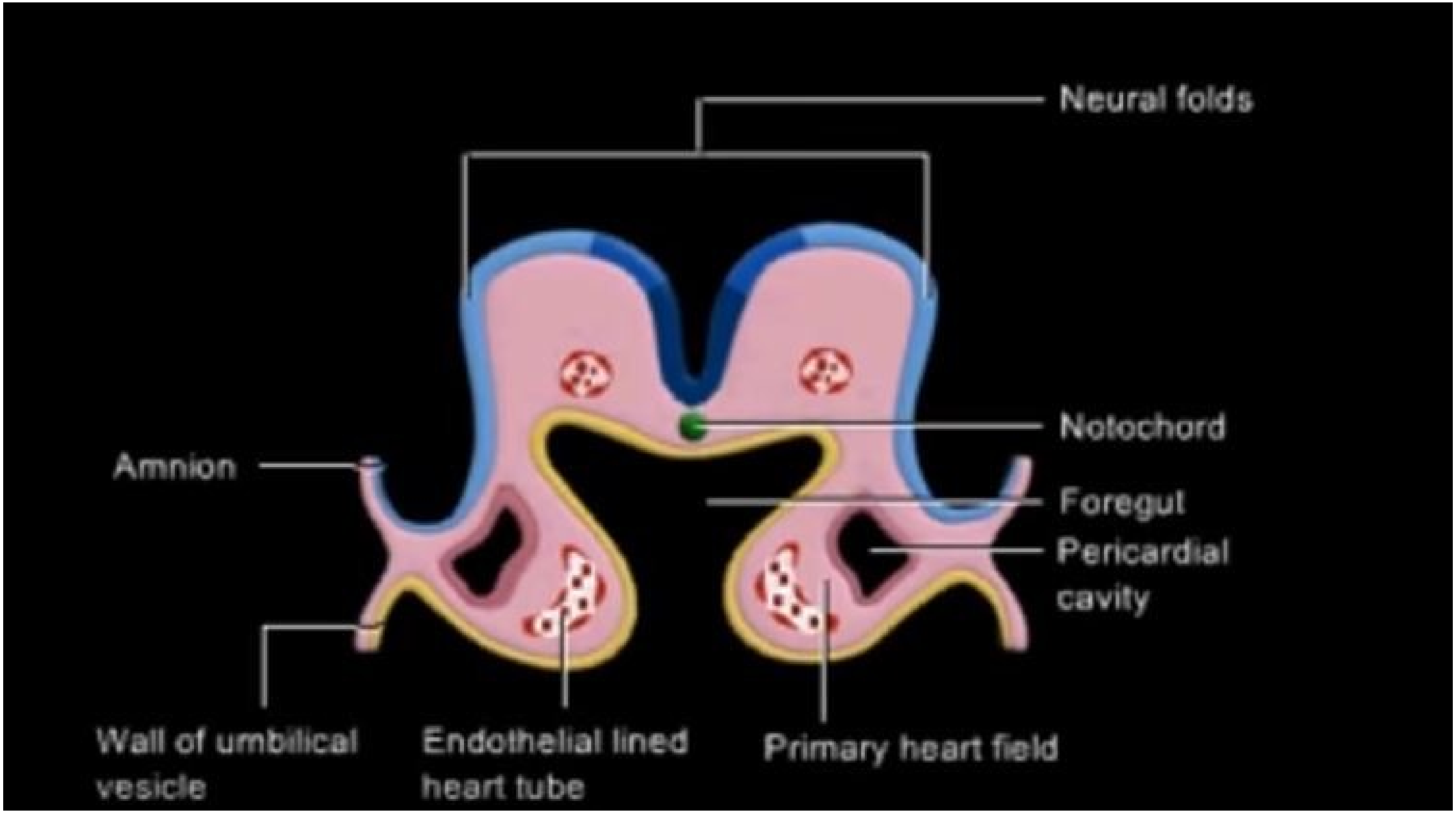


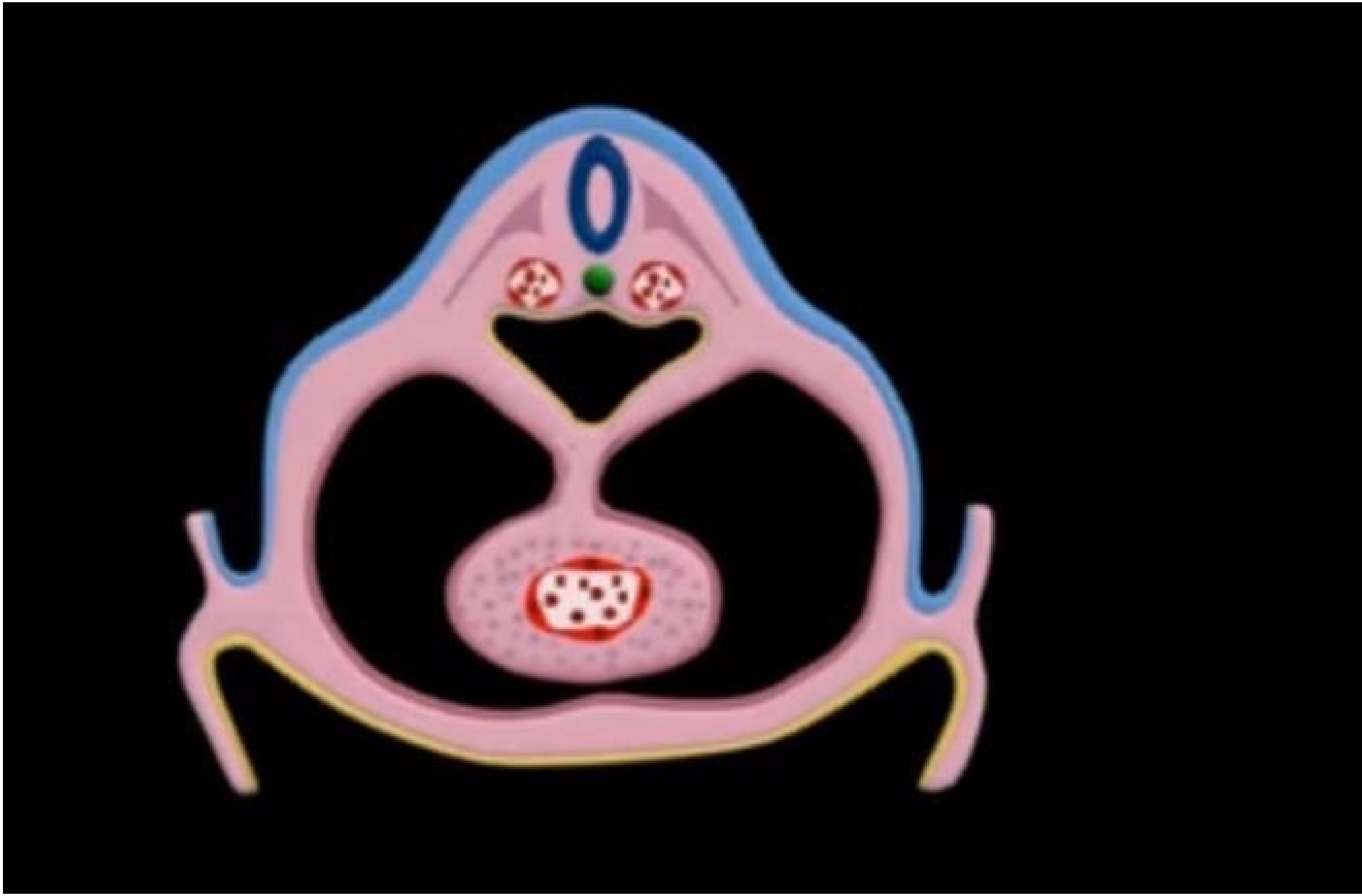





Developing forebrain
Foregut
Primitive heart tube
Septum transversum
Pericardial cavity
Oropharyngeal membrane




Neural folds
Notochord
Amnion
Foregut
Pericardial cavity
Wall of umbilical vesicle
Endothelial lined heart tube
Primary heart field

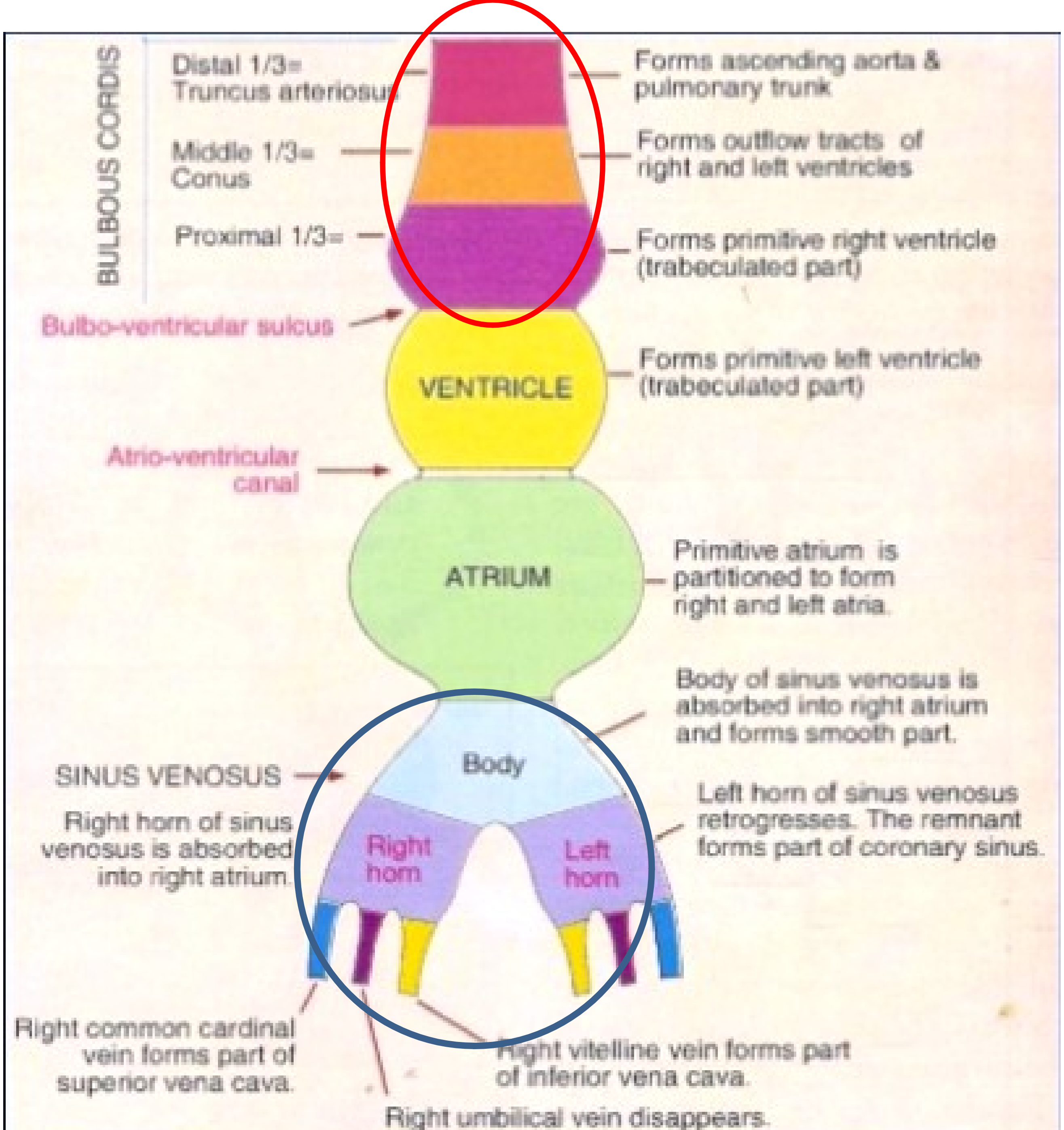


Arterial end of the heart tube

- **BULBUS CORDIS**
  - proximal part called the conus
  - a distal part called truncus arteriosus.
  - The truncus continues distally with the aortic sac.

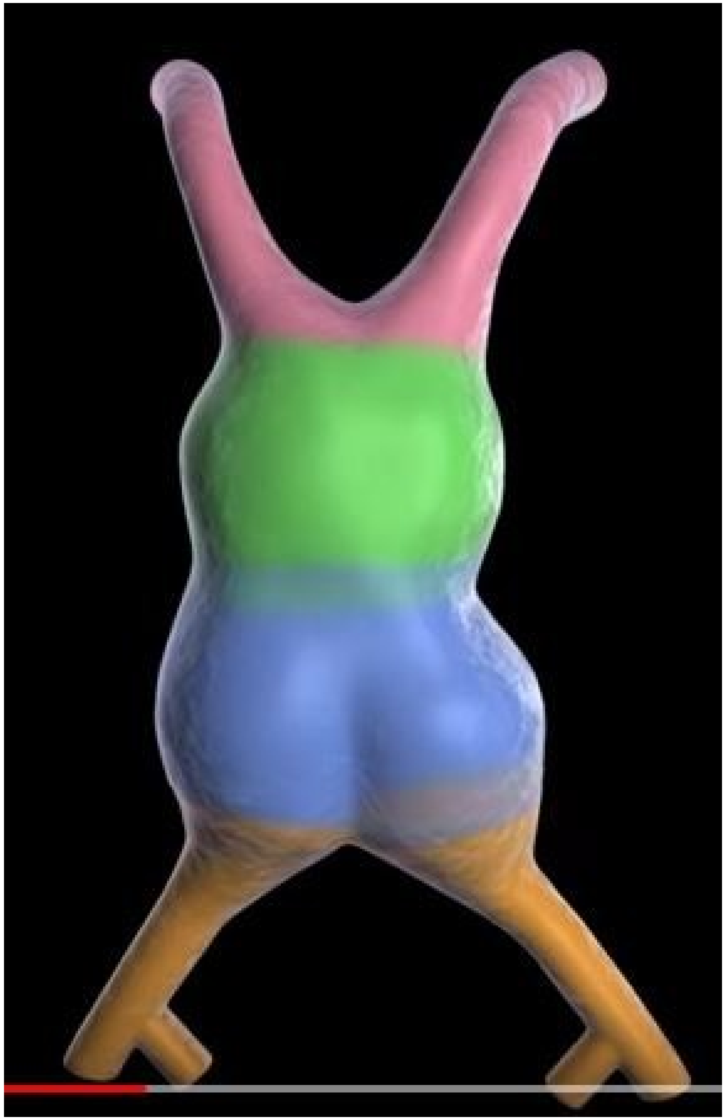
Venous end

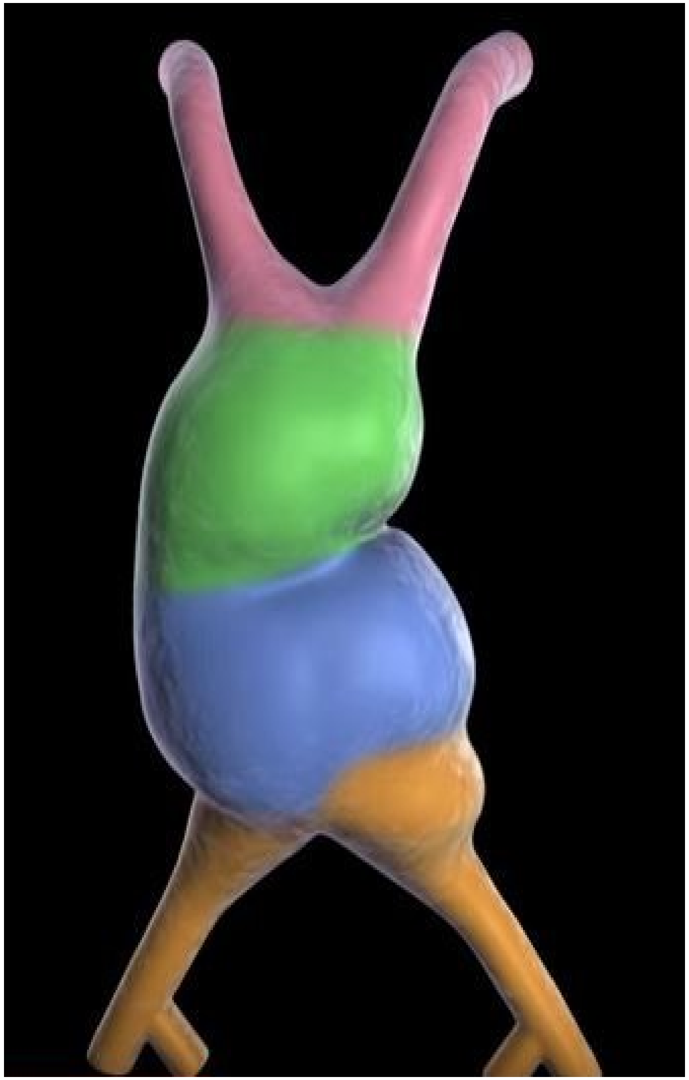
- The sinus venosus
- vitelline vein from the yolksac
- umbilical vein from the placenta
- common cardinal vein from the bodywall



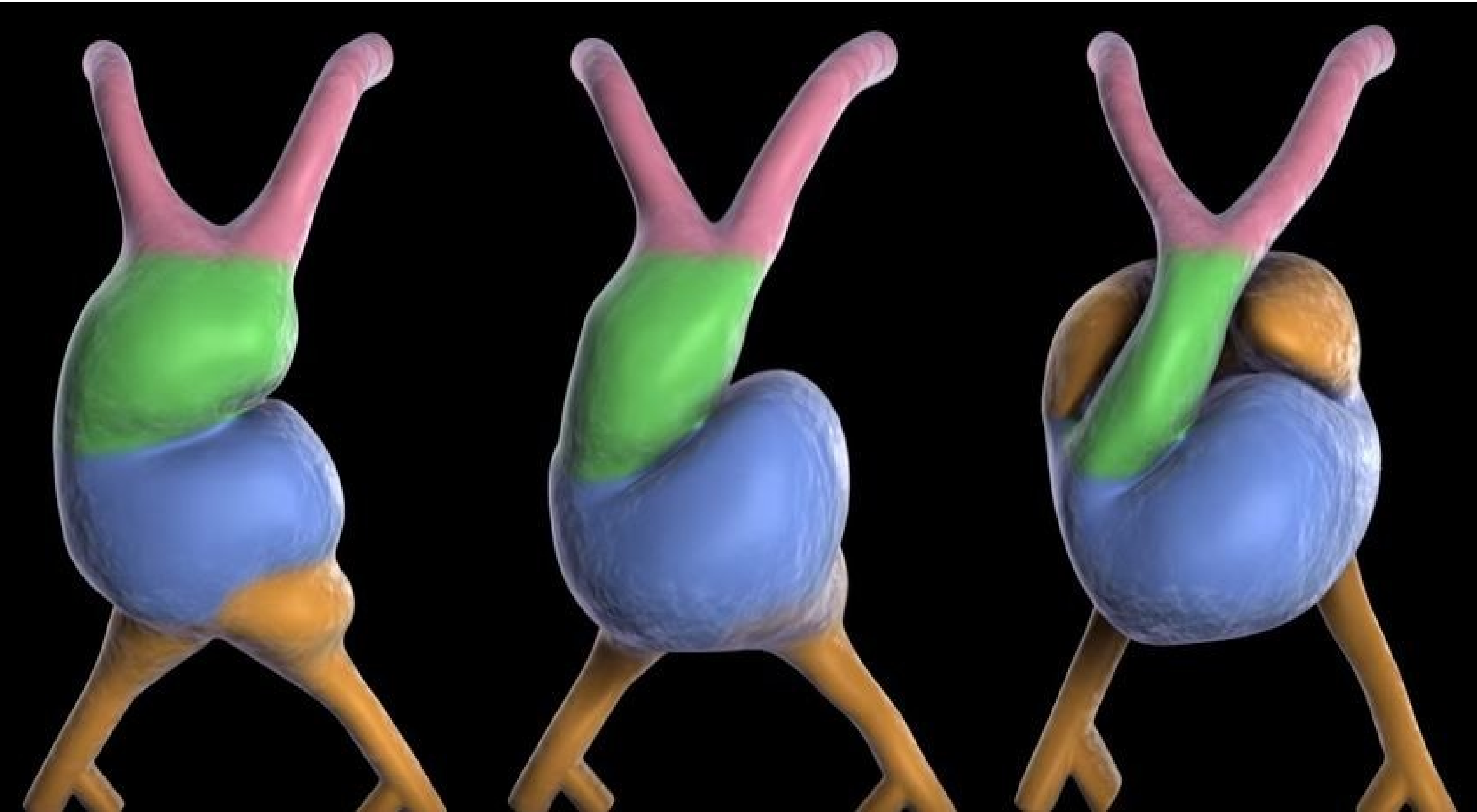
BULBOUS CORDIS
Distal 1/3=
Truncus arteriosus
Middle 1/3=
Conus
Proximal 1/3=
Forms ascending aorta & pulmonary trunk
Forms outflow tracts of right and left ventricles
Forms primitive right ventricle (trabeculated part)
Bulbo-ventricular sulcus
VENTRICLE
Forms primitive left ventricle (trabeculated part)
Atrio-ventricular canal
ATRIUM
Primitive atrium is partitioned to form right and left atria.
Body of sinus venosus is absorbed into right atrium and forms smooth part.
SINUS VENOSUS
Body
Right horn of sinus venosus is absorbed into right atrium.
Right horn
Left horn
Left horn of sinus venosus retrogresses. The remnant forms part of coronary sinus.
Right common cardinal vein forms part of superior vena cava.
Right vitelline vein forms part of inferior vena cava.
Right umbilical vein disappears.

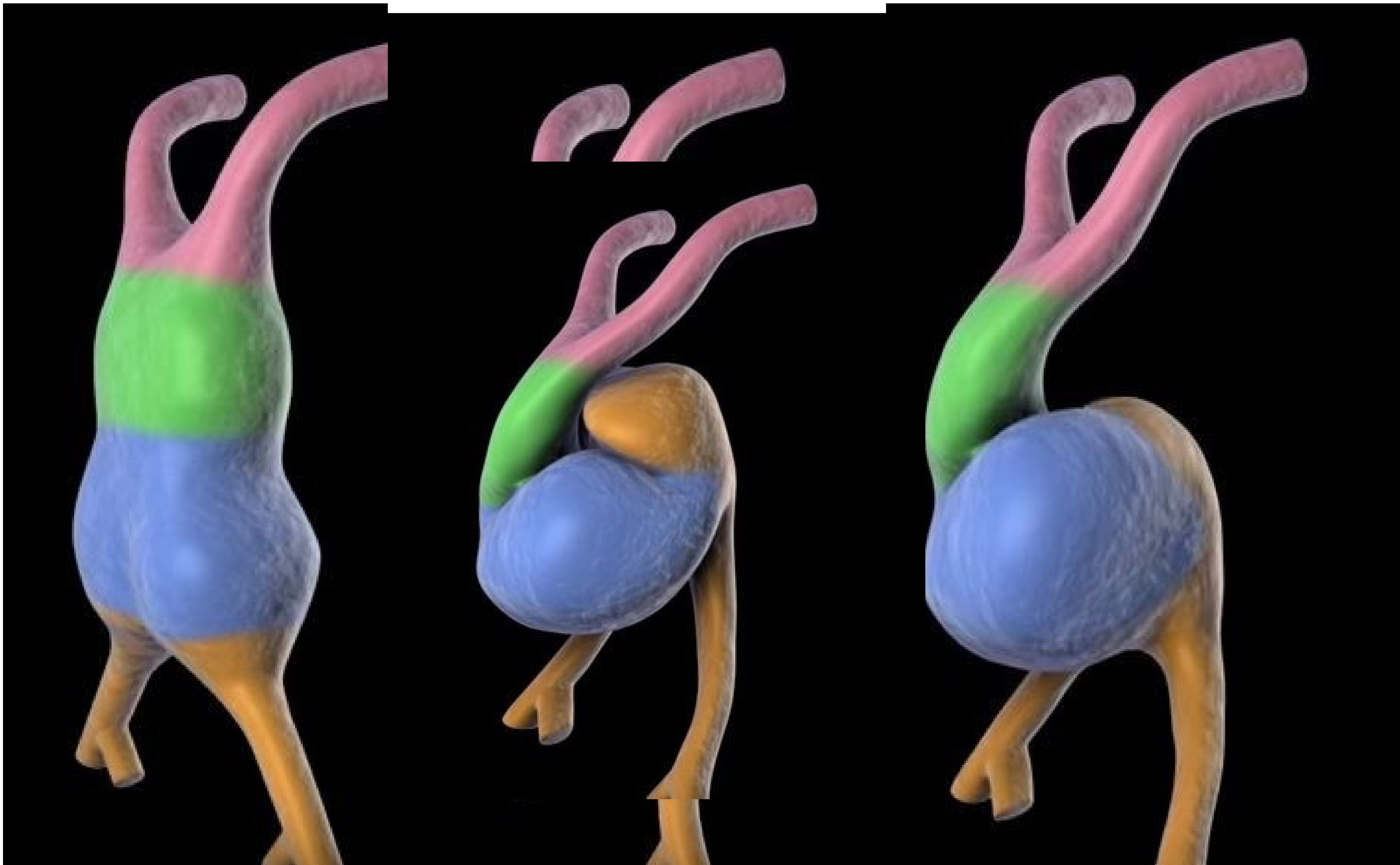
Looping





Looping



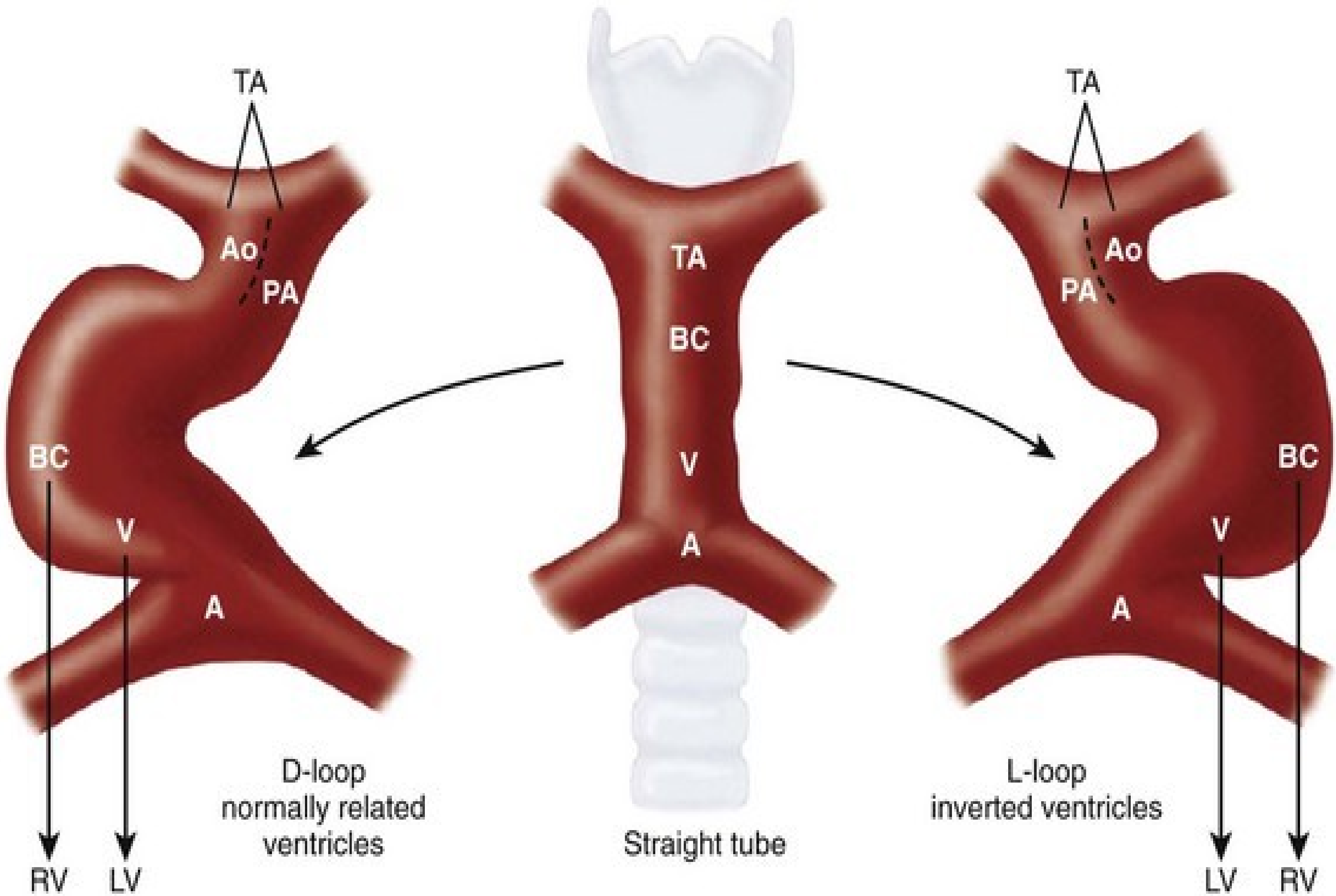


Mechanism of looping

- Differential growth of the heart tube in comparison with foregut
- Differential growth within the heart tube itself
- Posterior, leftward, slower growth and **anterior, rightward, faster growth** resulting in **RIGHTWARD LOOPING**

- Bending of the heart tube at the inflow as well as within the ventricular segment

- eventually positions the inflow and future left ventricular segments posteriorly and to the left, with the future right ventricle and outflow segments anteriorly and to the right


TA
Ao
PA
BC
V
A
RV
LV
D-loop
normally related
ventricles
TA
BC
V
A
Straight tube
TA
Ao
PA
BC
V
A
L-loop
inverted ventricles
LV
RV

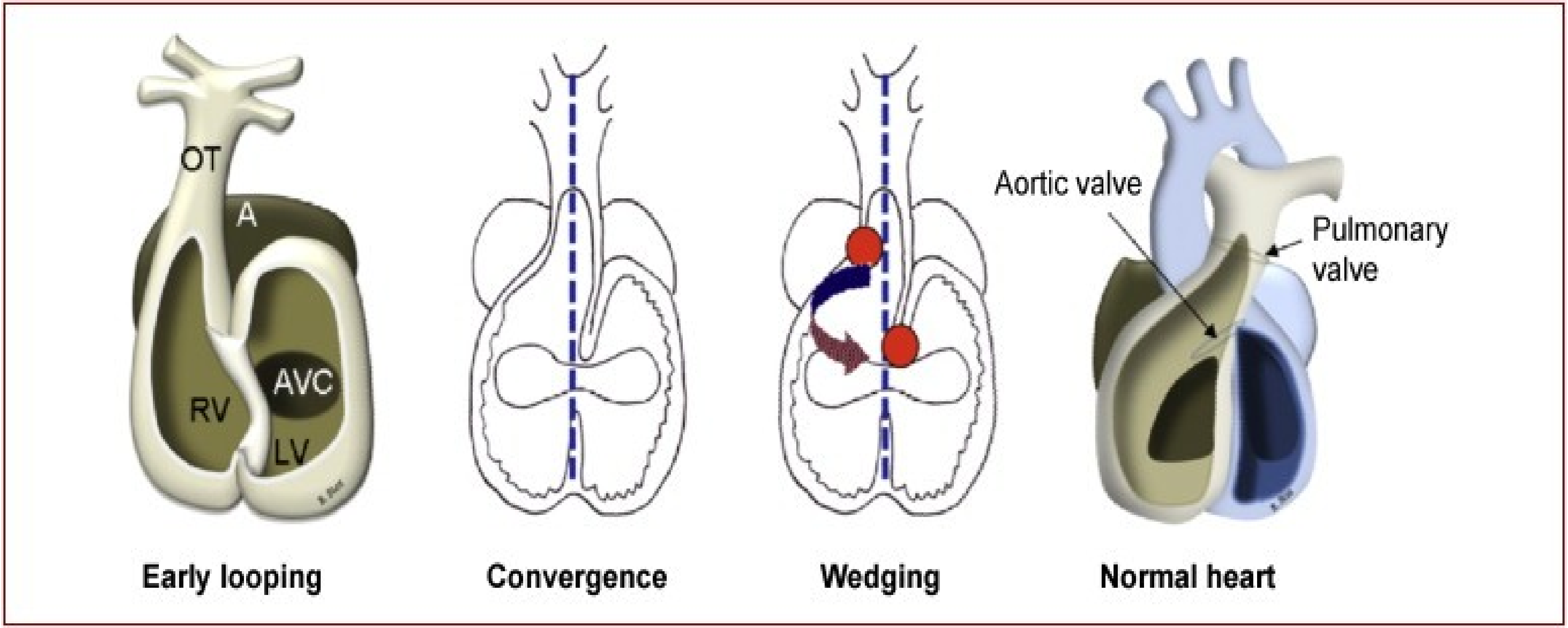
Convergence

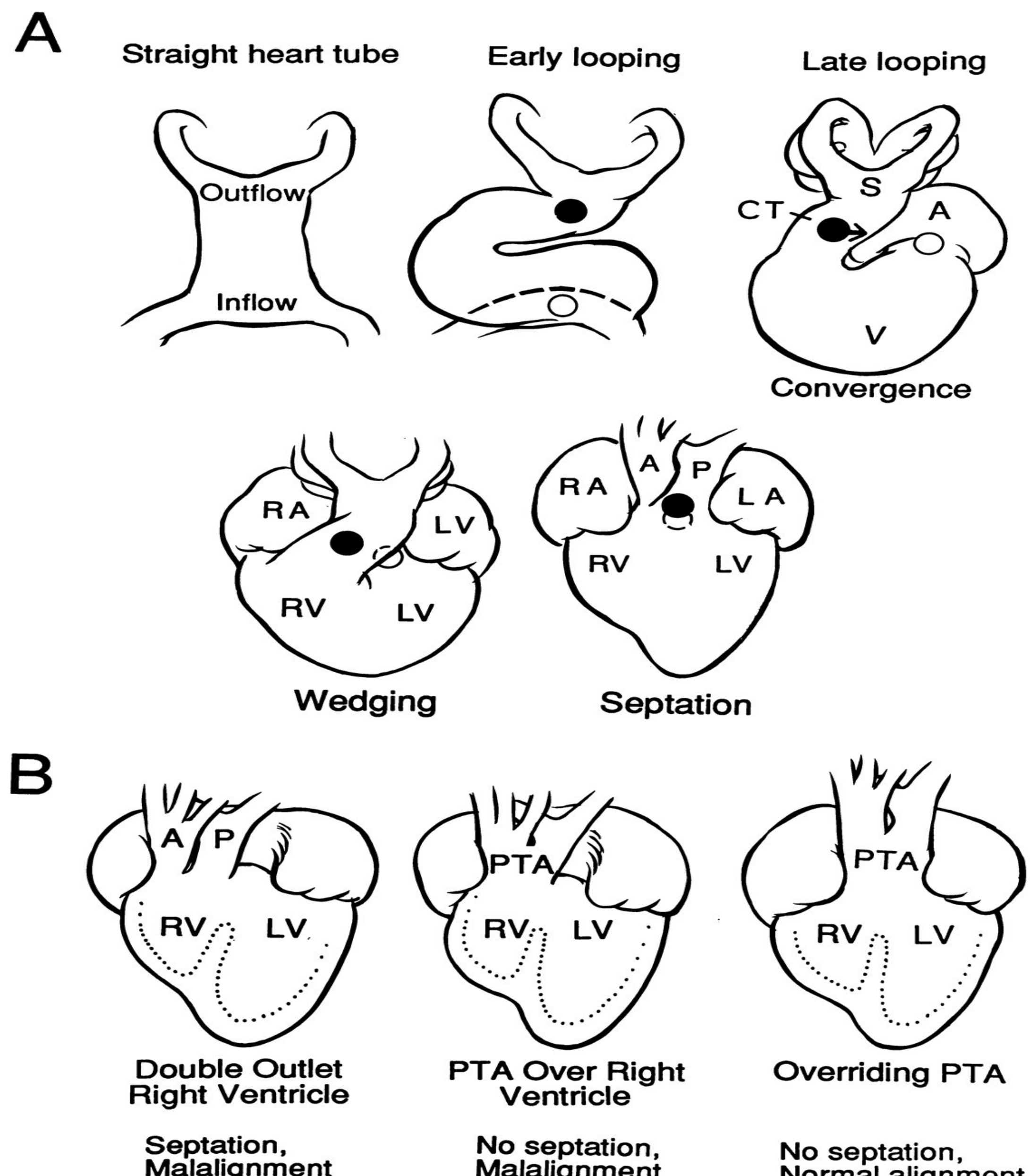
- Movement of the outflow tract and the atrioventricular canal into a more midline position
- Alignment

Wedging

- Seperation (septation) of the primitive ventricles and outflow tract into systemic (aorta) and pulmonary (pulmonary artery) trunks is created by a process called wedging
- The counterclockwise rotation of the outflow tract with movement of the future aortic valve position behind the pulmonary trunk

Convergence and Wedging




A
Straight heart tube
Outflow
Inflow
Early looping
Late looping
S
CT
A
V
Convergence
RA
LV
RV
LV
Wedging
A
P
RA
LA
RV
LV
Septation
B
A
P
RV
LV
Double Outlet
Right Ventricle
Septation,
Malalignment
PTA
RV
LV
PTA Over Right
Ventricle
No septation,
Malalignment
PTA
RV
LV
Overriding PTA
No septation,
Normal alignment

Myocardial Compaction

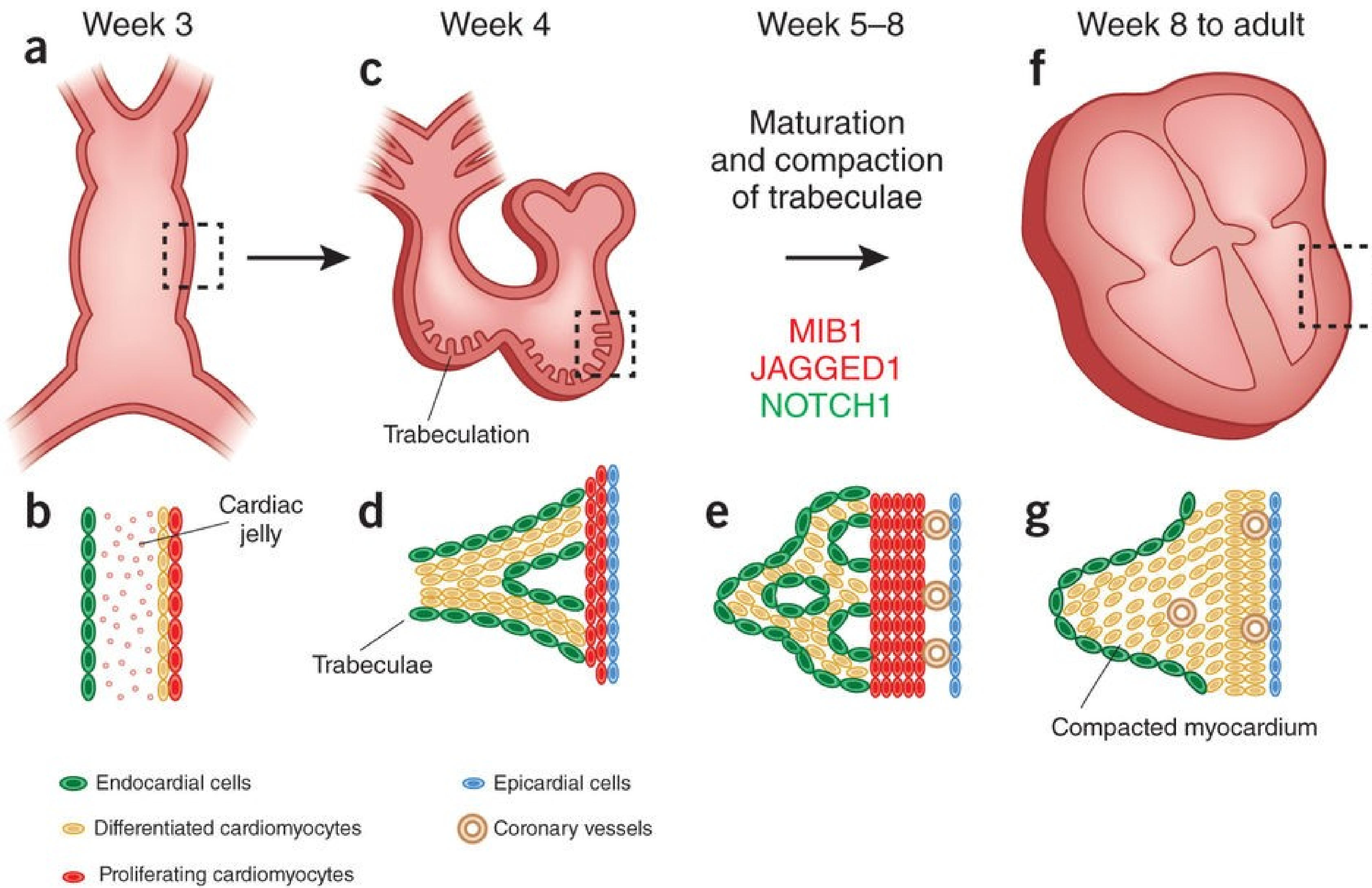
- Emergence of trabeculations
- Trabecular remodelling

Emergence of trabeculations

- Emerge after looping of the primitive heart tube
- At the end of the fourth week of gestation
- Trabeculation patterns are ventricle-specific
- trabeculations in the LV are generally thicker and the corresponding intertrabecular spaces larger

Trabecular remodeling

- After completion of ventricular septation at 8 weeks of gestation in
- Increase in ventricular volumes results in compression of the trabeculations with an increase in the thickness of the compacted myocardium
- Compaction process coincides with the invasion of epicardial coronary arteries


Week 3
Week 4
Week 5–8
Week 8 to adult
a
b
c
d
e
f
g
Maturation
and compaction
of trabeculae
MIB1
JAGGED1
NOTCH1
Trabeculation
Cardiac
jelly
Trabeculae
Compacted myocardium
Endocardial cells
Differentiated cardiomyocytes
Proliferating cardiomyocytes
Epicardial cells
Coronary vessels

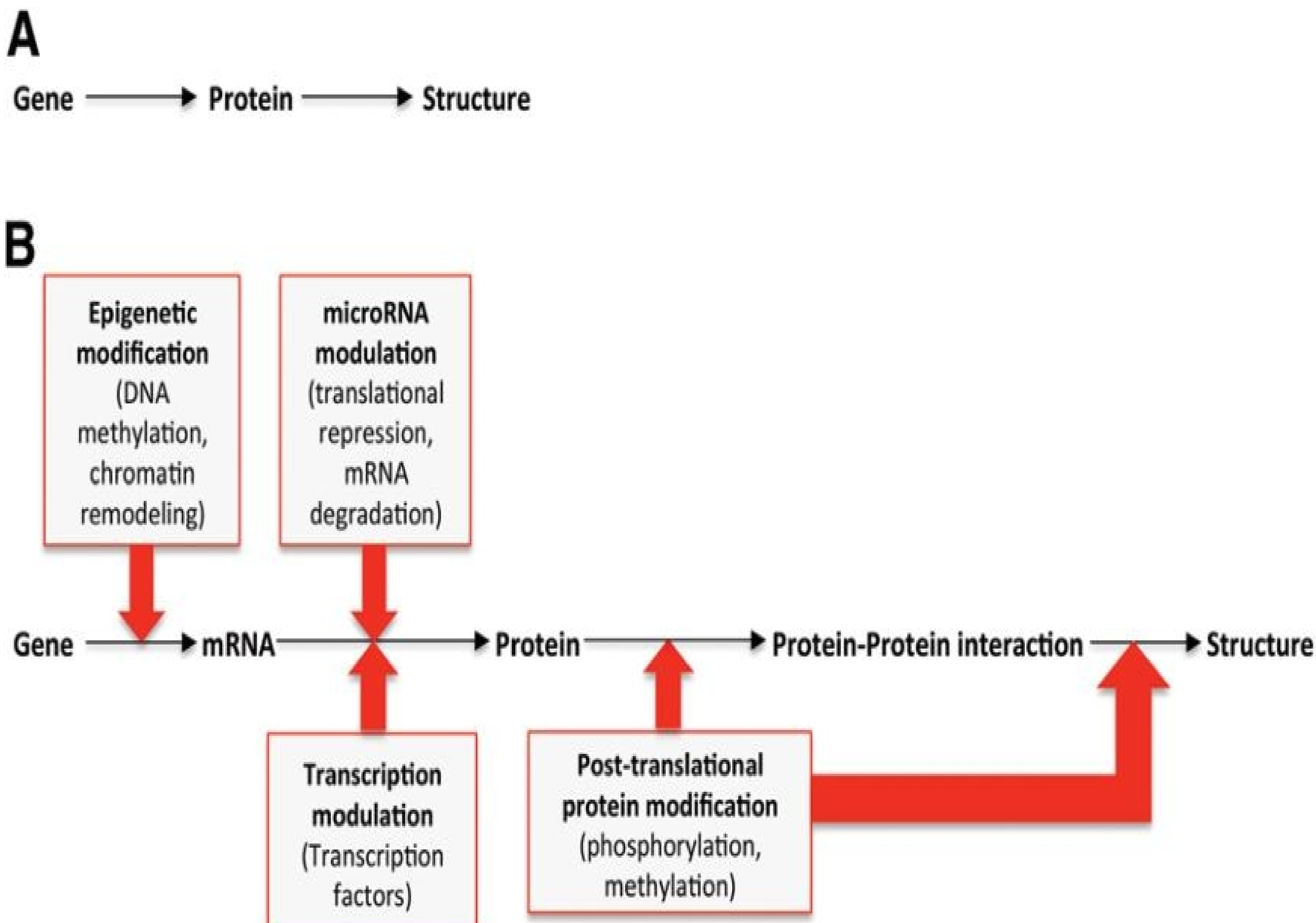

A
B
C
At 6 weeks:
Abundant fine trabeculations
At 8 weeks:
Trabeculae start to solidify
Early foetal period:
Compaction almost completed
The process of compaction

Evolution of human heart

- Progressive displacement of the inflow structures from a caudal position to a dorsal (fishes) and cephalad (reptiles) position.
- Septation of the atrium in a right and a left cavity (amphibians).
- Development of the right ventricle (RV) from the proximal part of the conus arteriosus.

- Septation starting at the interventricular groove separating the left from RV (crocodiles).
- Development of a high-pressure left ventricle (LV) and a low-pressure RV.
- Disappearance of the sinus venosus and the conus arteriosus (birds and mammals).

Molecular development of heart


A
Gene
Protein
Structure
B
Epigenetic modification (DNA methylation, chromatin remodeling)
microRNA modulation (translational repression, mRNA degradation)
Gene
mRNA
Protein
Protein-Protein interaction
Structure
Transcription modulation (Transcription factors)
Post-translational protein modification (phosphorylation, methylation)

Genes in induction of crescent

- Anterior (cranial) endoderm induces a heart-forming region by inducing the transcription factor **NKX2.5**.
- The signals require secretion of **BMPs 2 and 4** secreted by the endoderm and lateral plate mesoderm.
- Concomitantly, the activity of **WNT proteins (3a and 8)** secreted by the neural tube, must be blocked because they normally inhibit heart development.
- The combination of **BMP activity and WNT inhibition** by crescent and cerberus causes expression of NKX2.5.

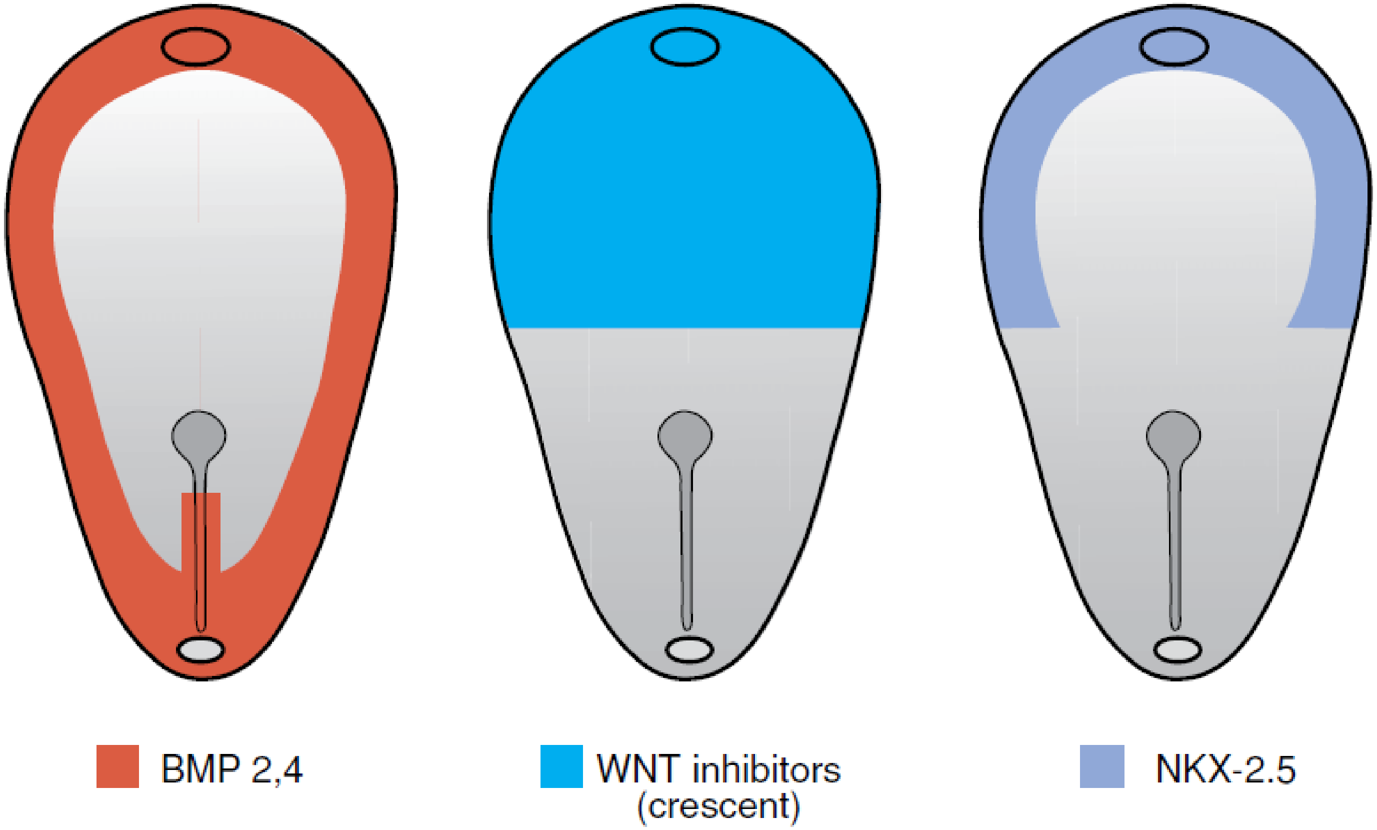
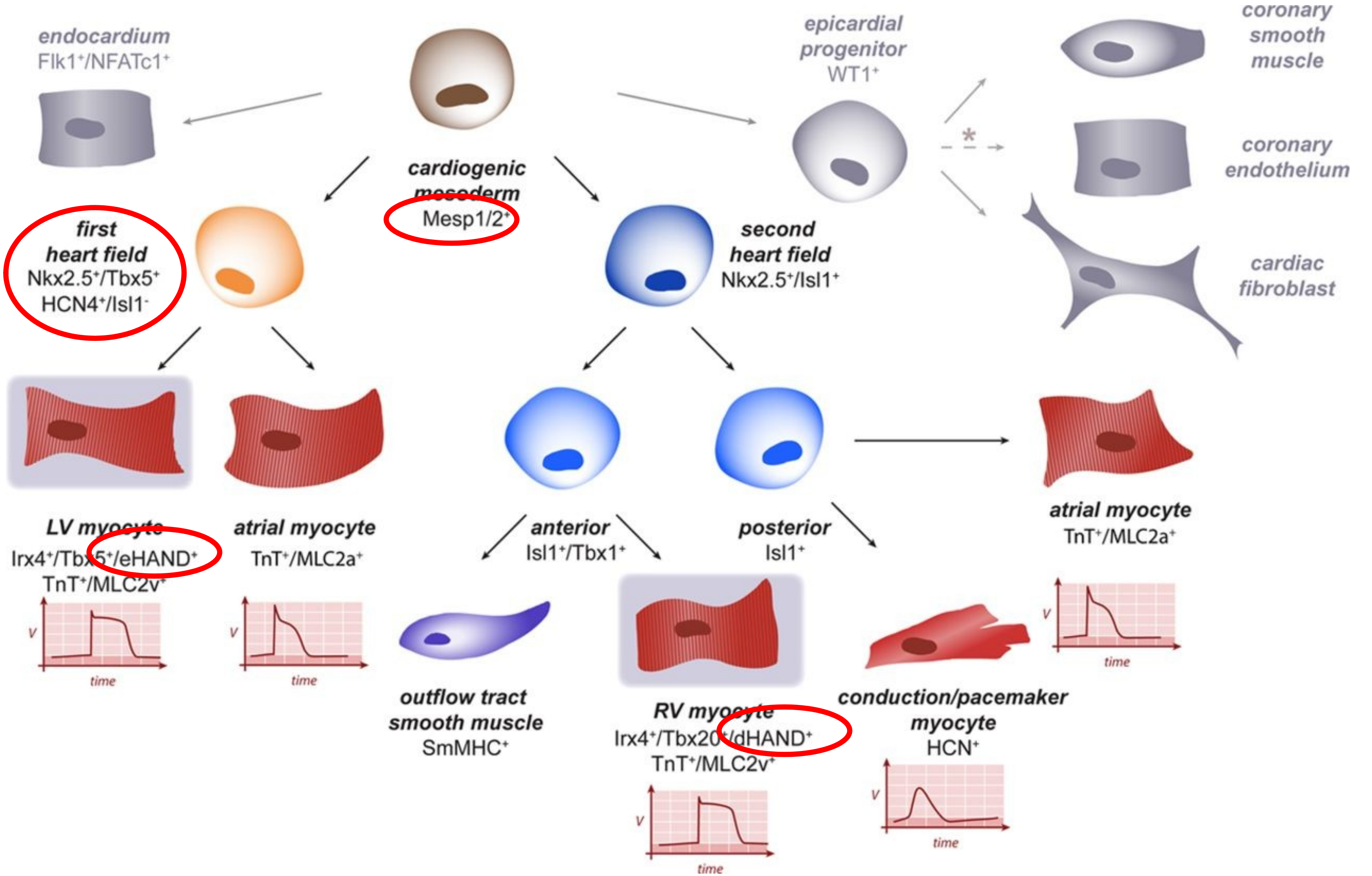
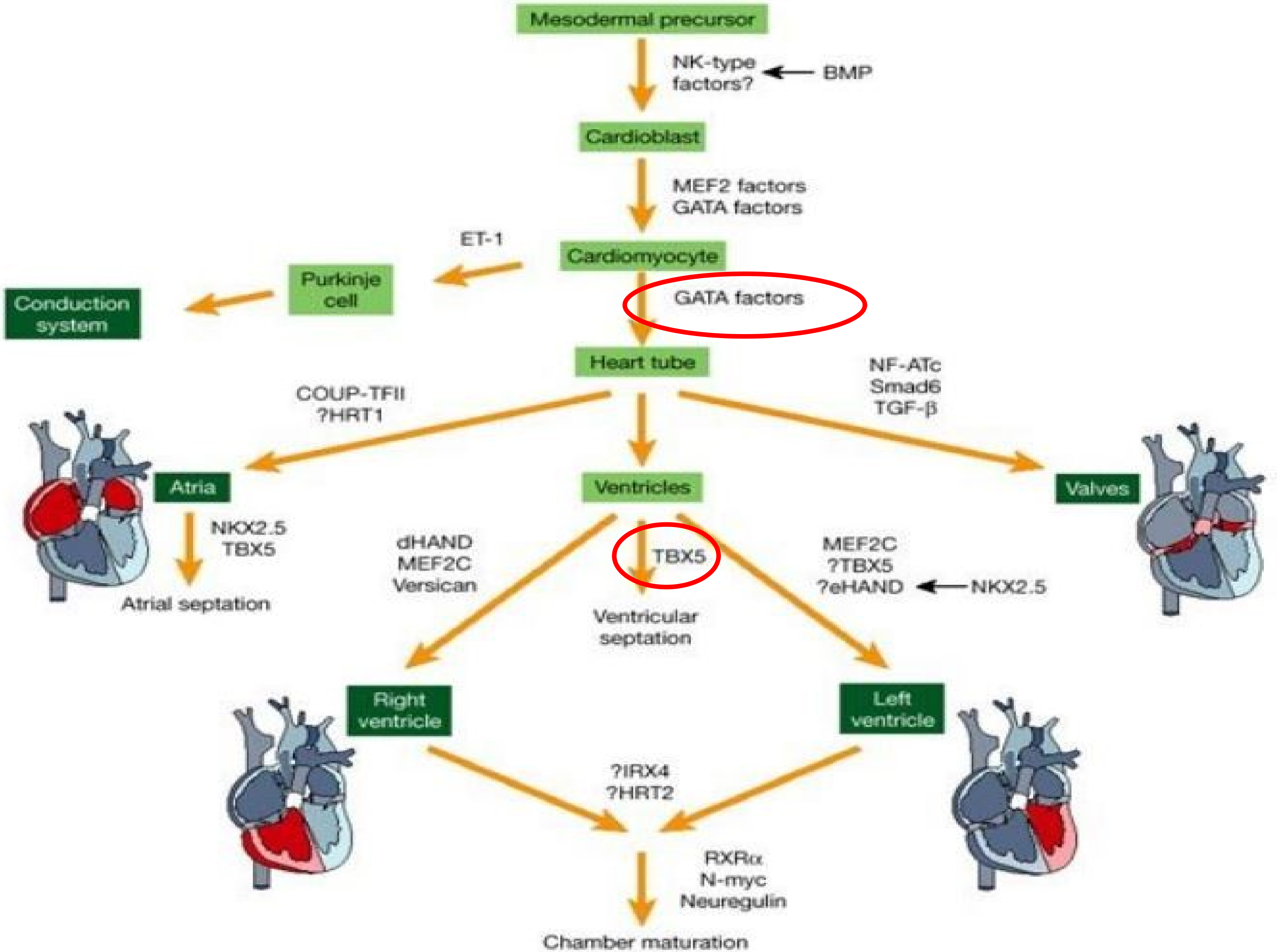


Figure 11.9 Heart induction. BMPs secreted in the posterior portion of the primitive streak and periphery of the embryo, in combination with inhibition of *WNT* expression by *crescent* in the anterior half of the embryo, induce expression of *NKX2.5* in the heart forming region of the lateral plate mesoderm (splanchnic layer). *NKX2.5* is then responsible for heart induction.

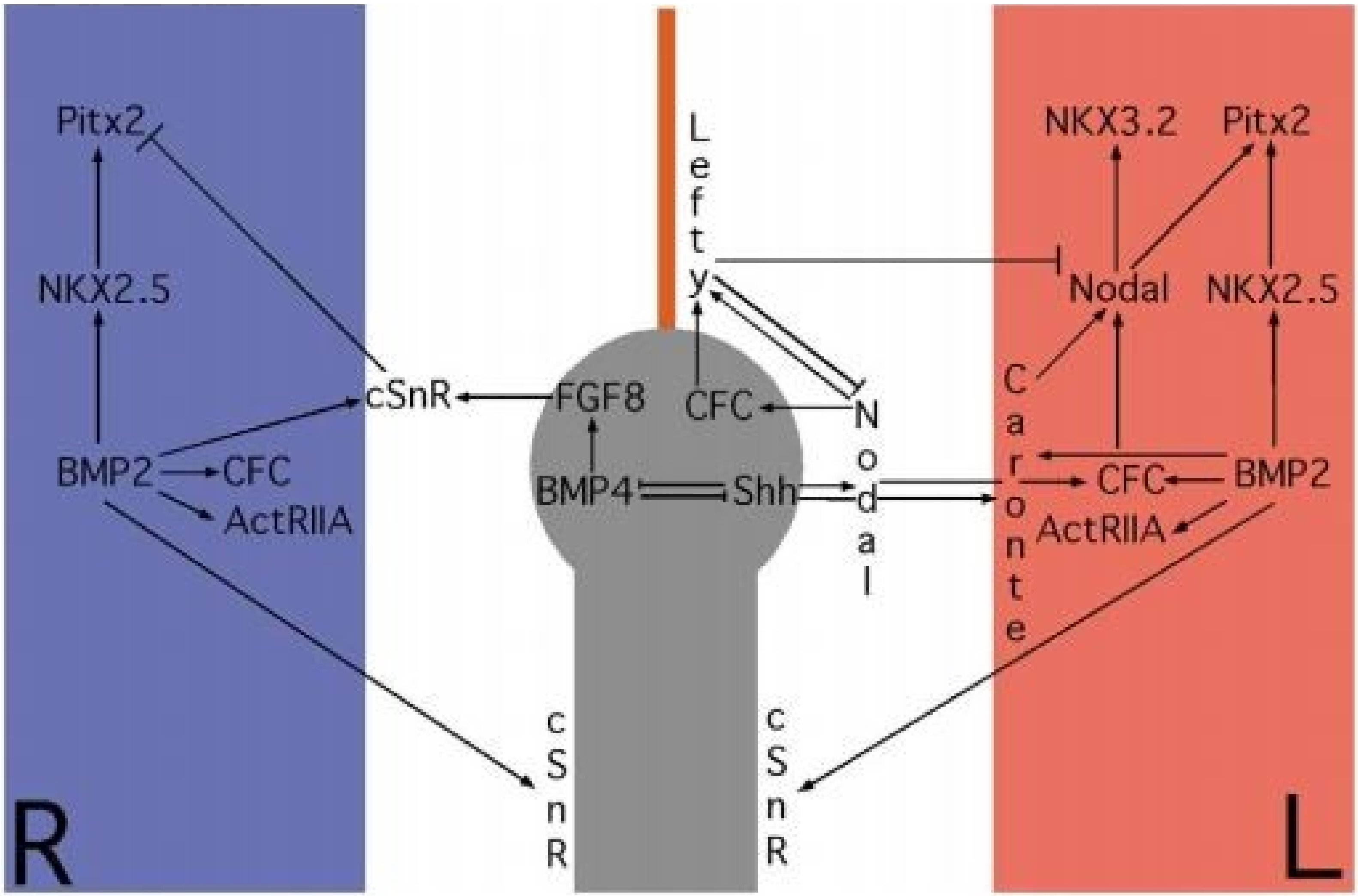
Genes in differentiation



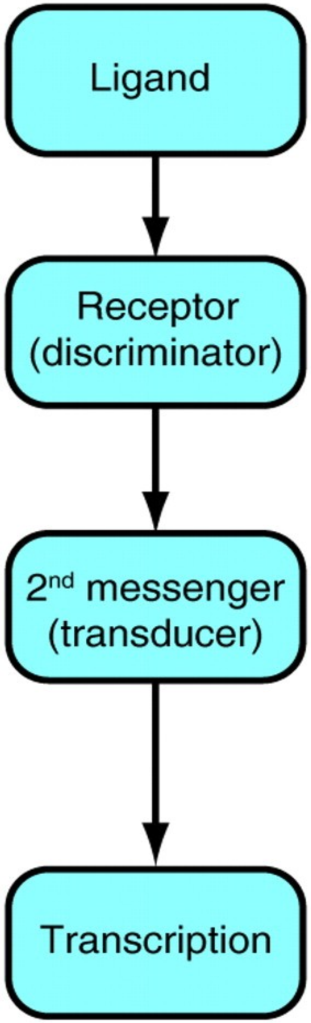


Mesodermal precursor
NK-type factors?
BMP
Cardioblast
MEF2 factors
GATA factors
ET-1
Cardiomyocyte
Purkinje cell
Conduction system
GATA factors
Heart tube
COUP-TFII
?HRT1
NF-ATc
Smad6
TGF-β
Atria
Ventricles
Valves
NKX2.5
TBX5
Atrial septation
dHAND
MEF2C
Versican
TBX5
Ventricular septation
MEF2C
?TBX5
?eHAND
NKX2.5
Right ventricle
Left ventricle
?IRX4
?HRT2
RXRα
N-myc
Neuregulin
Chamber maturation

Right left asymmetry



Signalling networks



NOTCH
BMP
WNT
FGF
SEMAPHORIN

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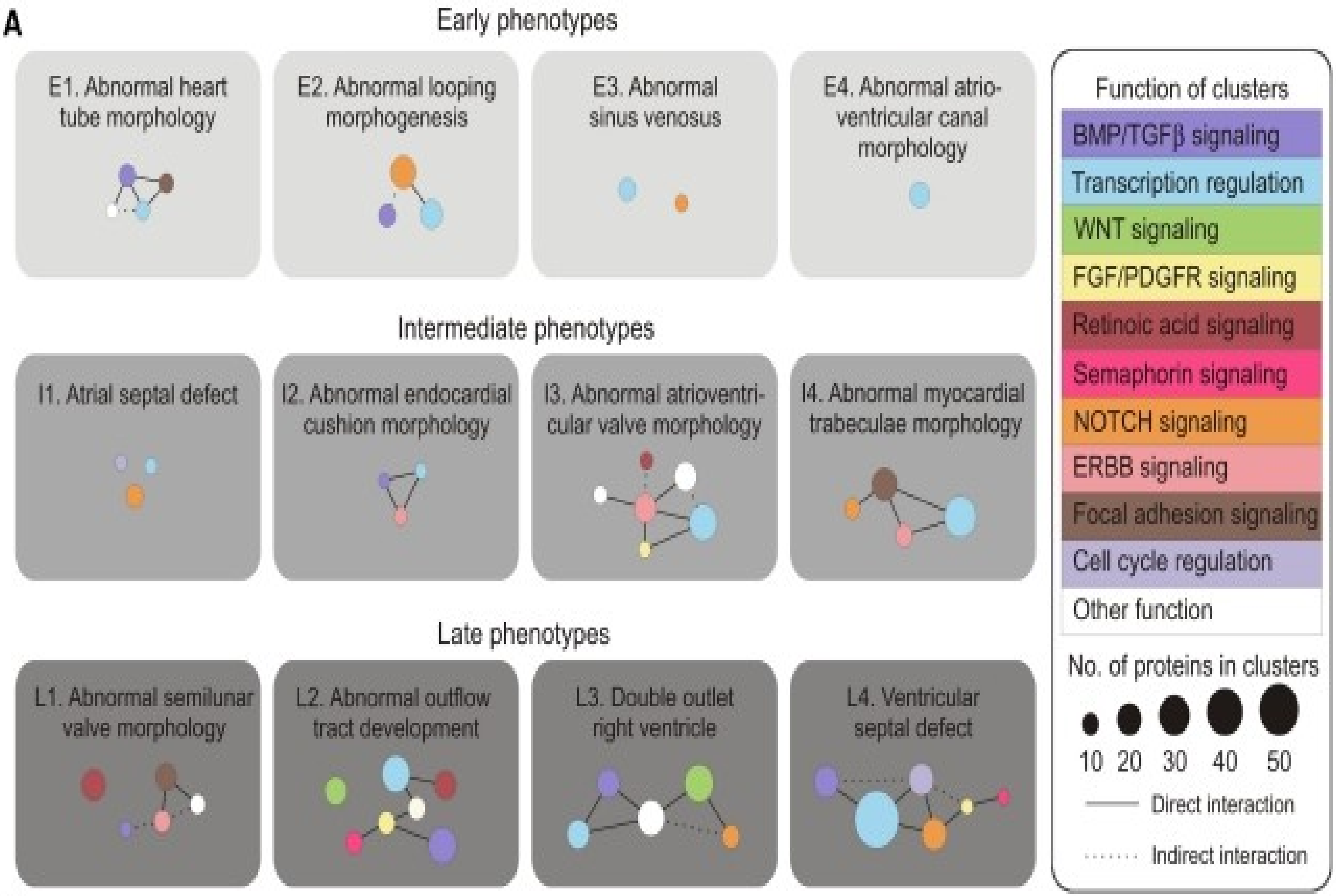
Dissecting spatio-temporal protein networks driving human heart development and related disorders

Kasper Lage,[a,1,2,3,4,5] Kjeld Møllgård,[6] Steven Greenway,[7] Hiroko Wakimoto,[7] Joshua M Gorham,[7] Christopher T Workman,[4] Eske Bendsen,[8] Niclas T Hansen,[4] Olga Rigina,[4] Francisco S Roque,[4,5] Cornelia Wiese,[9] Vincent M Christoffels,[9] Amy E Roberts,[10,11] Leslie B Smoot,[11] William T Pu,[11,12] Patricia K Donahoe,[1,2,3] Niels Tommerup,[13] Søren Brunak,[4,5] Christine E Seidman,[7] Jonathan G Seidman,[7] and Lars A Larsen[b,13]

Abstract

Go to:

Aberrant organ development is associated with a wide spectrum of disorders, from schizophrenia to congenital heart disease, but systems-level insight into the underlying processes is very limited. Using heart morphogenesis as general model for dissecting the functional architecture of organ development, we combined detailed phenotype information from deleterious mutations in 255 genes with high-confidence experimental interactome data, and coupled the results to thorough experimental validation. Hereby, we made the first systematic analysis of spatio-temporal protein networks driving many stages of a developing organ identifying several novel signaling modules. Our results show that organ development relies on surprisingly few, extensively recycled, protein modules that integrate into complex higher-order networks.


A
Early phenotypes
E1. Abnormal heart tube morphology
E2. Abnormal looping morphogenesis
E3. Abnormal sinus venosus
E4. Abnormal atrio-ventricular canal morphology
Intermediate phenotypes
I1. Atrial septal defect
I2. Abnormal endocardial cushion morphology
I3. Abnormal atrioventricular valve morphology
I4. Abnormal myocardial trabeculae morphology
Late phenotypes
L1. Abnormal semilunar valve morphology
L2. Abnormal outflow tract development
L3. Double outlet right ventricle
L4. Ventricular septal defect
Function of clusters
BMP/TGFβ signaling
Transcription regulation
WNT signaling
FGF/PDGFR signaling
Retinoic acid signaling
Semaphorin signaling
NOTCH signaling
ERBB signaling
Focal adhesion signaling
Cell cycle regulation
Other function
No. of proteins in clusters
10
20
30
40
50
Direct interaction
Indirect interaction

B

Developmental abnormalities

- From Fertilization to Primitive Heart Tube

  -Abnormal development at this stage of embryogenesis results in embryonic death because of the critical nature of the early circulation to the further growth

Abnormal left right signalling

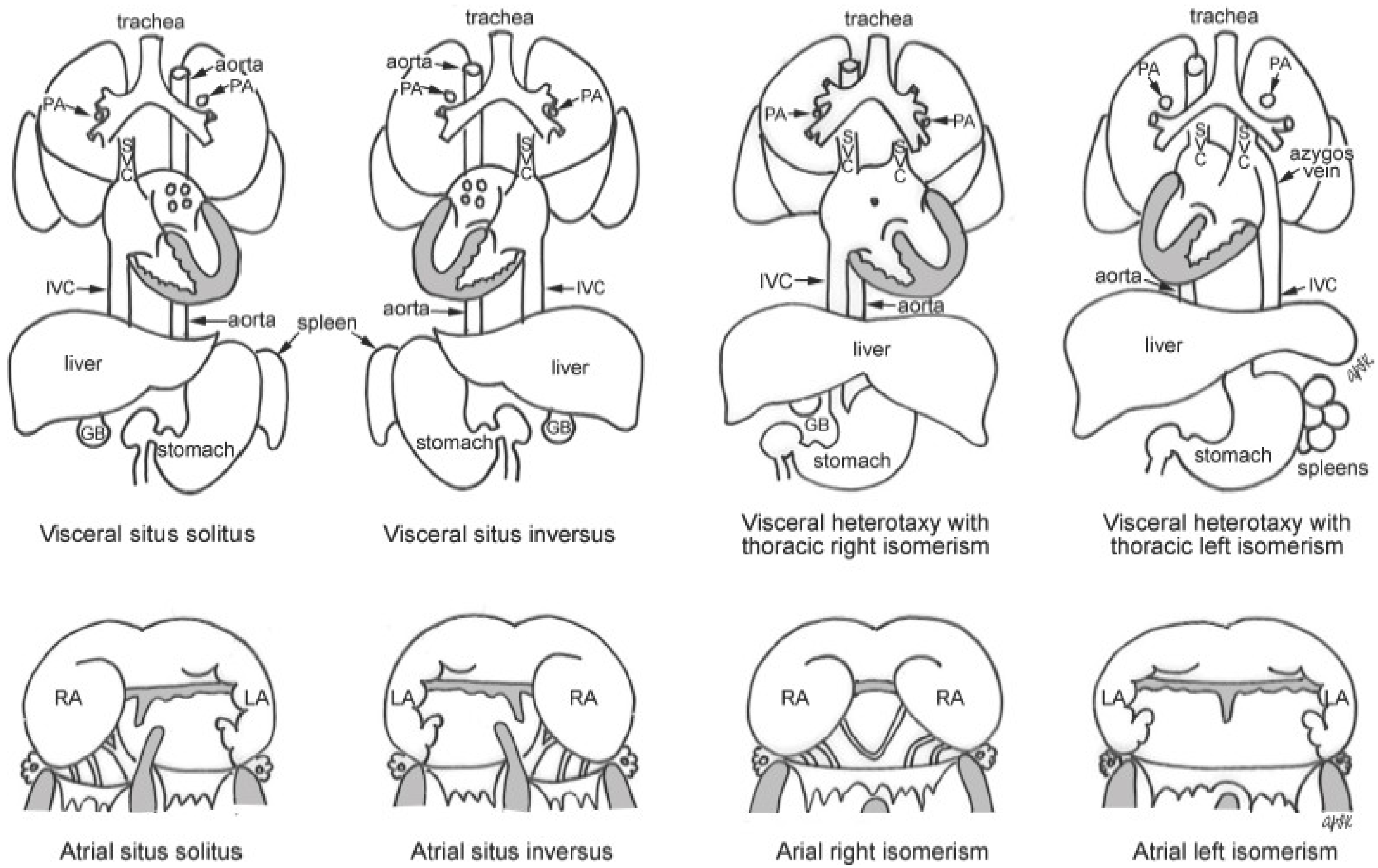
- HETEROTAXY SYNDROMES

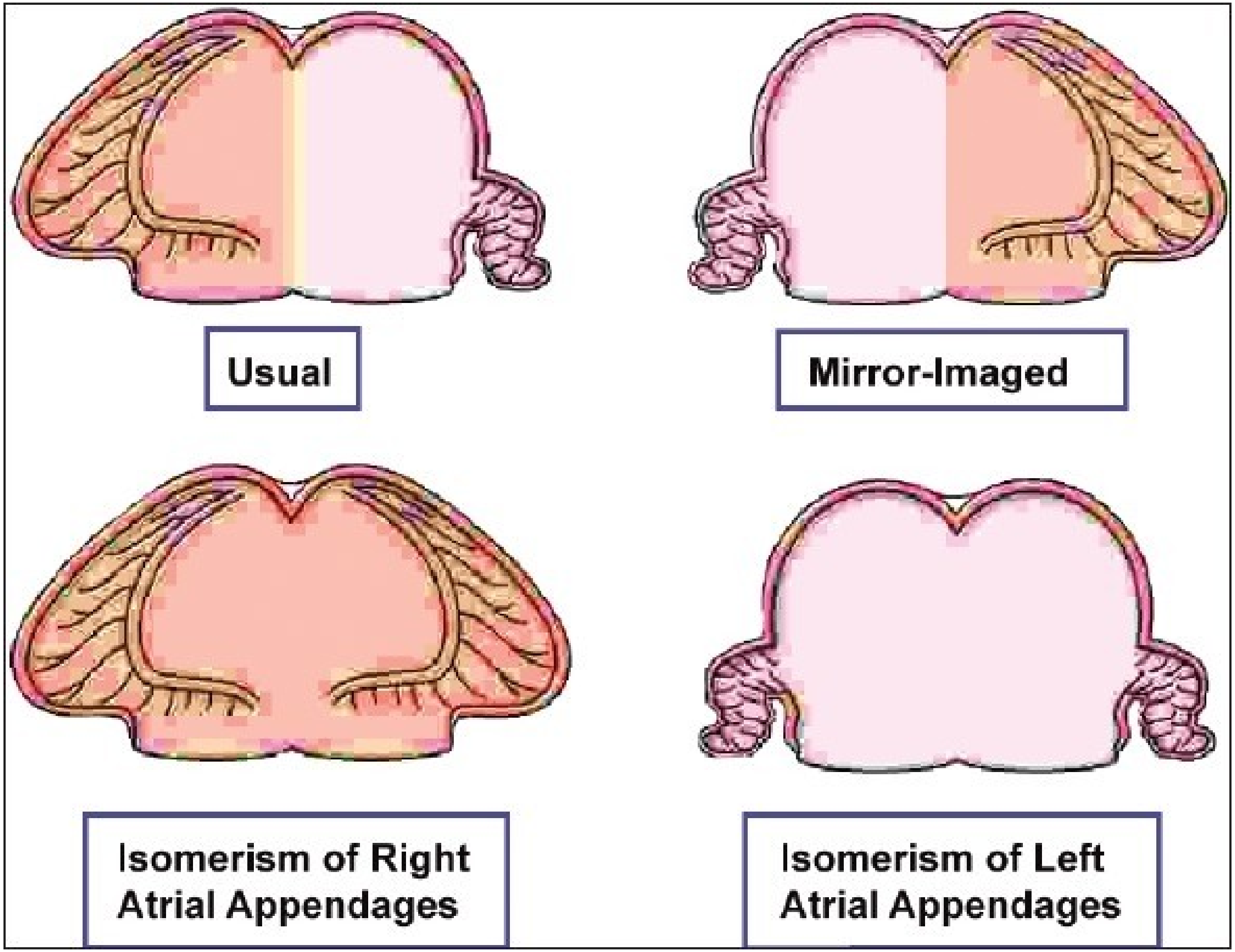
    -Right Isomerism

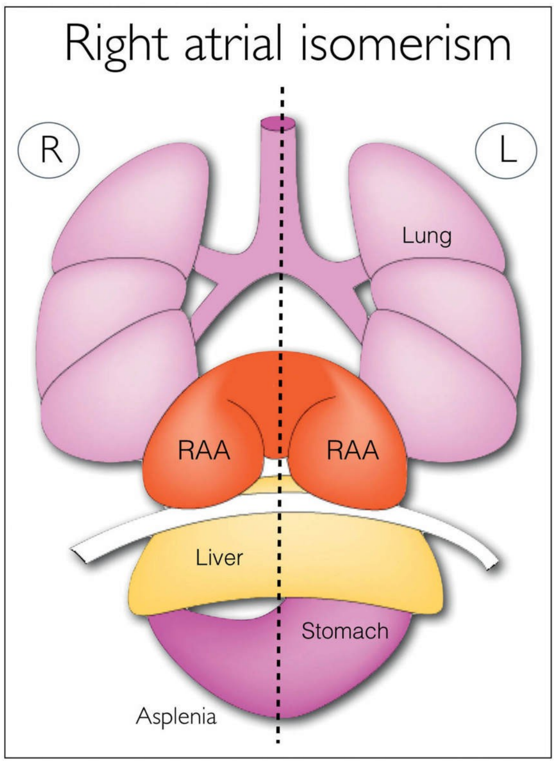
    -Left Isomerism

    -Situs inversus with dextrocardia

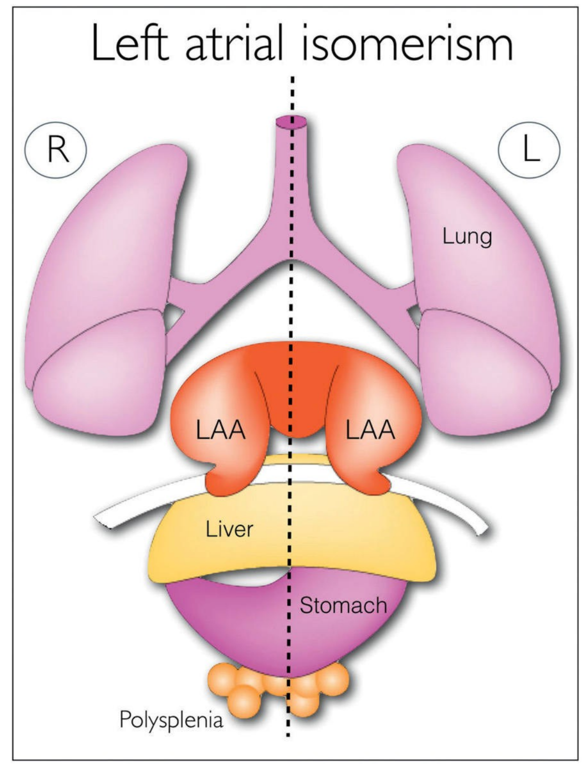
Heterotaxy spectrum



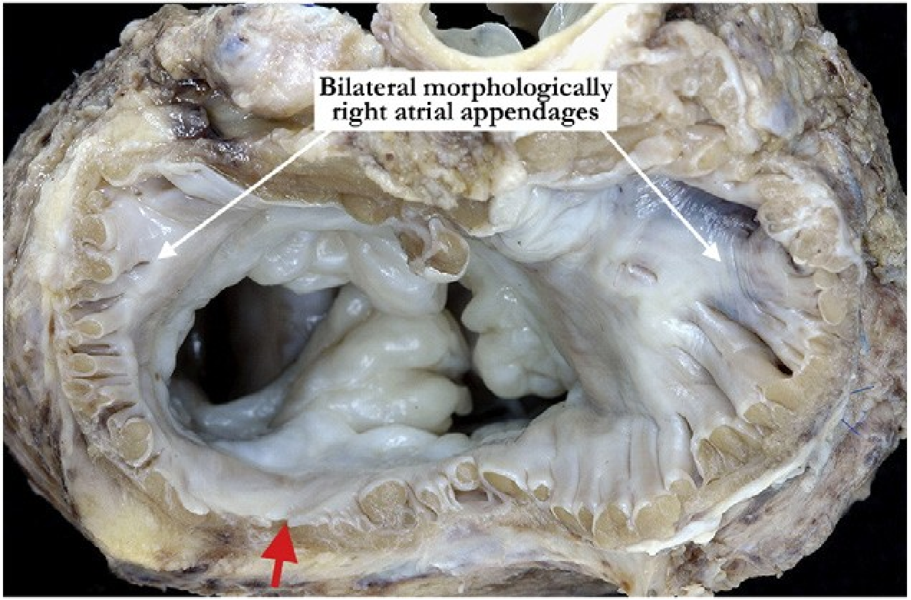

Usual
Mirror-Imaged
Isomerism of Right
Atrial Appendages
Isomerism of Left
Atrial Appendages

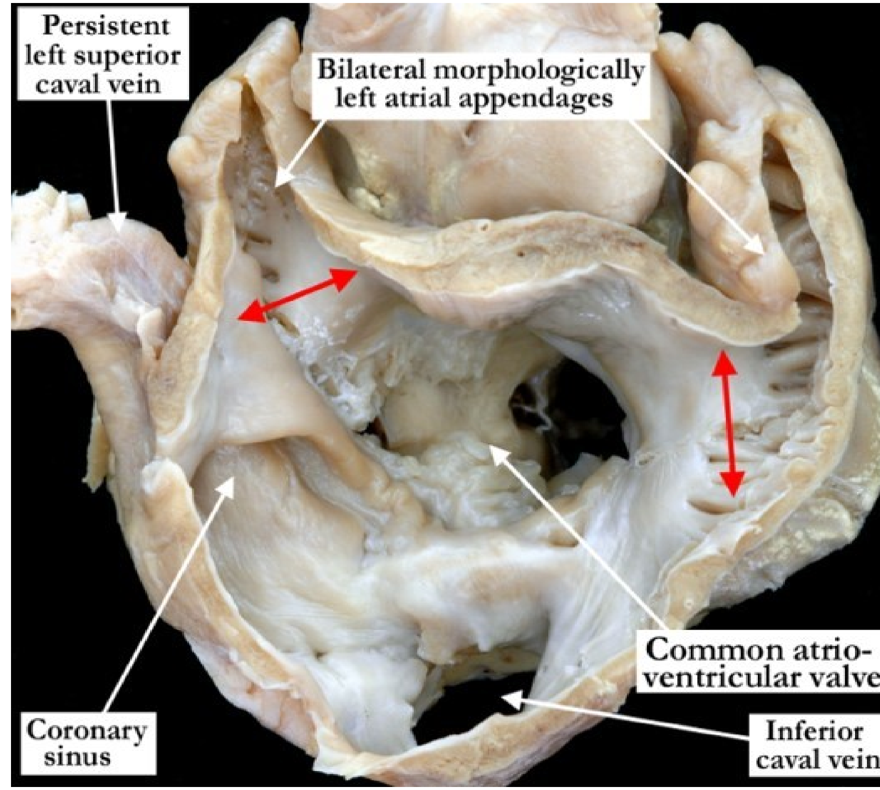


Right atrial isomerism
R
L
Lung
RAA
RAA
Liver
Stomach
Asplenia



Left atrial isomerism
R
L
Lung
LAA
LAA
Liver
Stomach
Polysplenia





Morphological features

- triangular
- broad base appendage
- extensive pectinate muscle
- presence of terminal crest.

Morphological features

- tubular narrow based appendage
- limited pectinate muscle
- and no terminal crest.

Characteristics of left and right isomerism		
Characteristic	Left atrial isomerism	Right atrial isomerism
Atrial appendages	2 left atrial appendages	2 right atrial appendages
Multiple cardiac defects	Present	Present (more severe and frequent)
Congenital heart block	Present	Unlikely
Pulmonary	Bilateral bilobed lungs	Bilateral trilobed lungs
Polysplenia	Present	Not present
Asplenia	Not present	Present
Venous abnormality	Interruption of the IVC with azygous vein continuation	Malposition of IVC with IVC and aorta parallel on same side of the spine

Right Isomerism

- Cardiac :
  - The sinus nodes are paired because bilateral superior vena cavae are attached to bilateral morphologic right atria.
  - The P-wave axis is normal because the right sinus node is usually the dominant atrial pacemaker
  - The atrioventricular conduction system is equipped with 2 nodes often connected by a sling of tissue
  - Supraventricular tachycardia is attributed to reentry between paired atrioventricular nodes.

Right Isomerism- Associations

- common atrium,
- common atrioventricular valve,
- Morphologic single ventricle,
- Functional single ventricle (hypoplasticright or left),
- pulmonary stenosis or atresia,
- absent coronary sinus
- total anomalous pulmonary venous connection
- bilateral ductus arteriosus.
- Ventricular and great arterial connections are usually discordant.

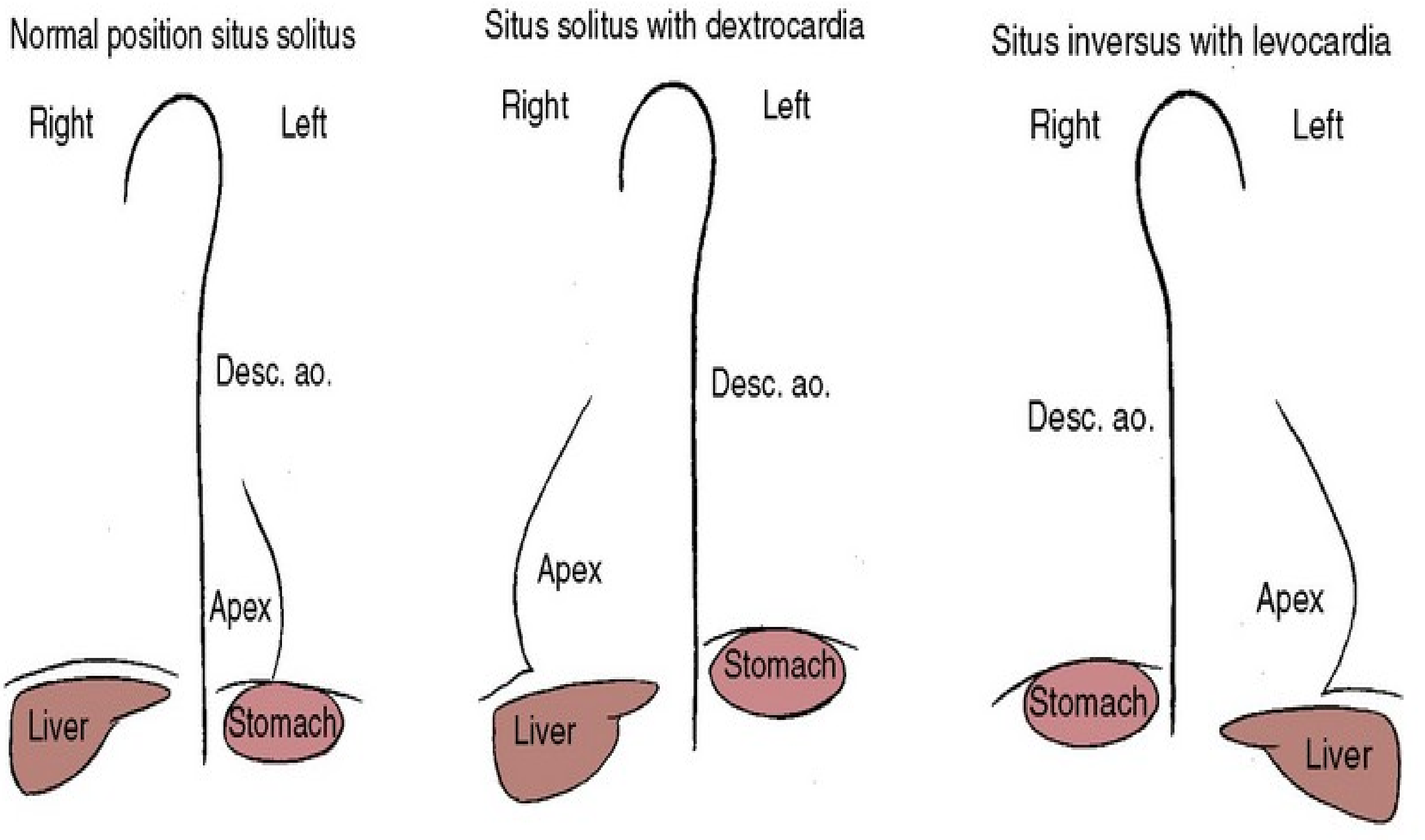
Left Isomerism

- More prevalent in women
- The pulmonary veins can be connected in a symmetric fashion, 2 to the right-sided atrium and 2 to the left-sided atrium
- The most distinctive and the most diagnostically useful clinical feature is **inferior vena caval interruption** with azygous continuation, in which the suprarenal segment of the inferior cava is absent, and the infrarenal segment continues as the azygos or hemiazygous vein
- **Fetal complete heart block** is presumptive evidence of in utero left isomerism

Left Isomerism

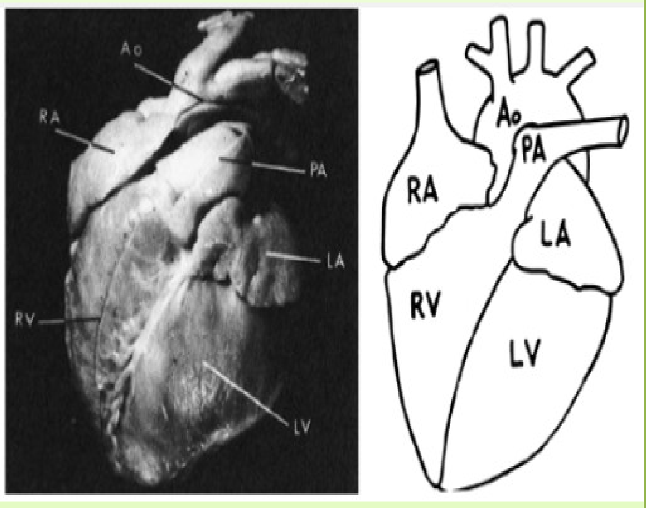
- Sinus node is absent or hypoplastic.
- The atrial pacemaker is therefore ectopic, and the P-wave axis is abnormal.
- The ectopic atrial pacemaker can shift from 1 site to another or may fire slowly (ectopic atrial bradycardia

Malpositions due to looping defects



Situs solitus with Dextrocardia

- Isolated dextrocardia with AV concordance and NRGA
- The base-to-apex axis points to the right, right hemidiaphragm is lower
- **The embryonic straight heart tube initially bends rightward (d-loop) but fails to move into the left chest.**
- Congenital heart defects:
  - ventricular septal defect
  - left SVC to the coronary sinus
  - coarctation of the aorta
  - secundum atrial septal defect
  - anomalous pulmonary venous connections

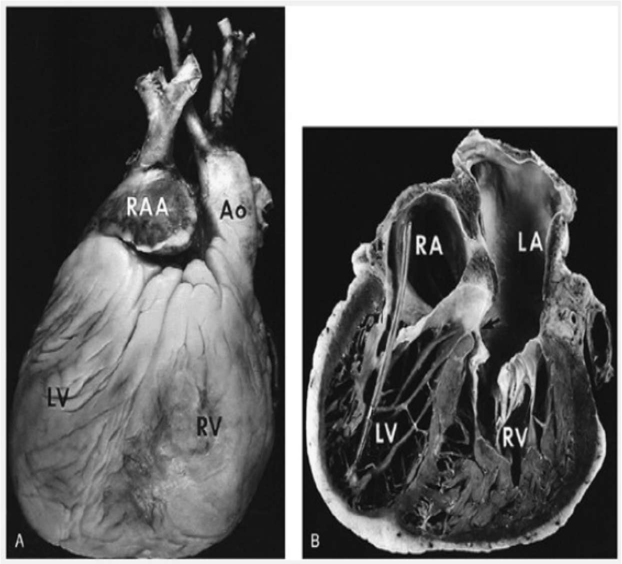


- ECG
  - atrial activation is normal, and the P-wave frontal plane axis is 70 to 80
  - the frontal plane QRS axis exhibits a rightward shift or right-axis deviation
  - a gradual and progressive reduction in the QRS R-wave voltage is observed

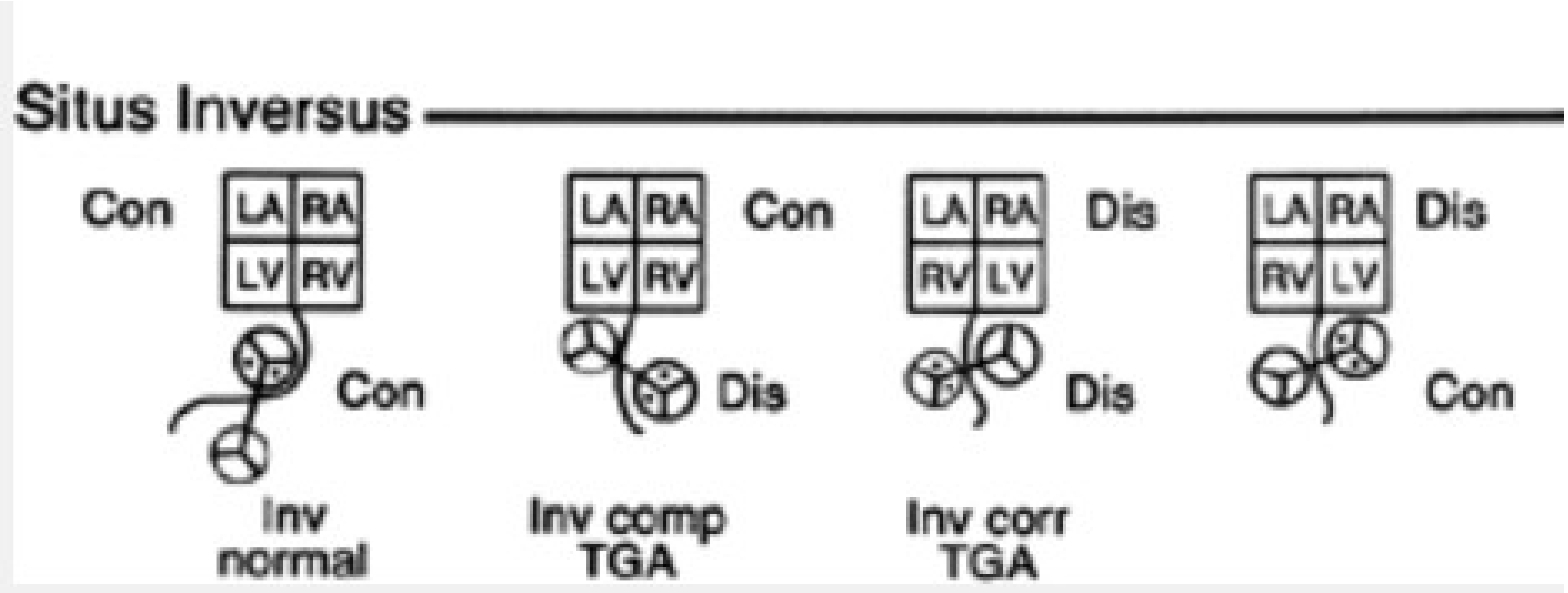
Corrected Transposition of the Great Arteries

- Isolated Dextrocardia with AV and VA Discordance and Left Anterior Aorta

- most common form of dextrocardia

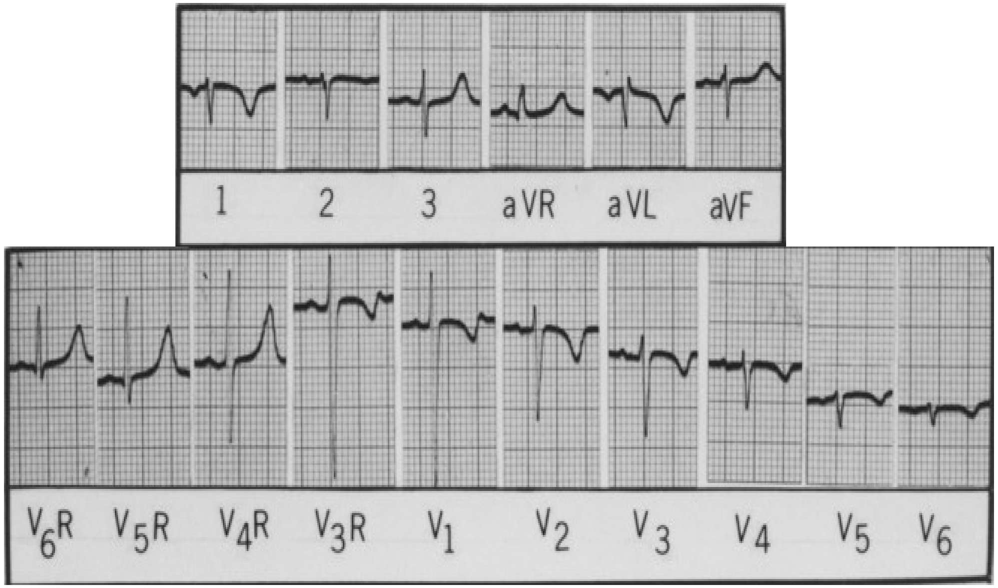


Situs Inversus



Situs inversus with Dextrocardia

- Incidence 1 in 8,000
- The thoracic and abdominal viscera are mirror images of normal
- morphologic right bronchus is concordant with the morphologic right atrium and a trilobed lung
  - usually occurs with a structurally normal heart



- **Situs inversus with Dextrocardia: reversed ventricular activation and reversed repolarization.**
  - **lead 1: QRS negative & the T wave inverted,**
  - **lead aVR resembles aVL and vice versa,**
  - **right precordial leads resemble leads from corresponding left precordial sites.**
  - **Septal Q waves appear in right**

Situs inversus with Dextrocardia Inverted Normally Related Great Arteries (Left Posterior Aorta)

- Situs inversus totalis with persistence of normal AV and VA connections

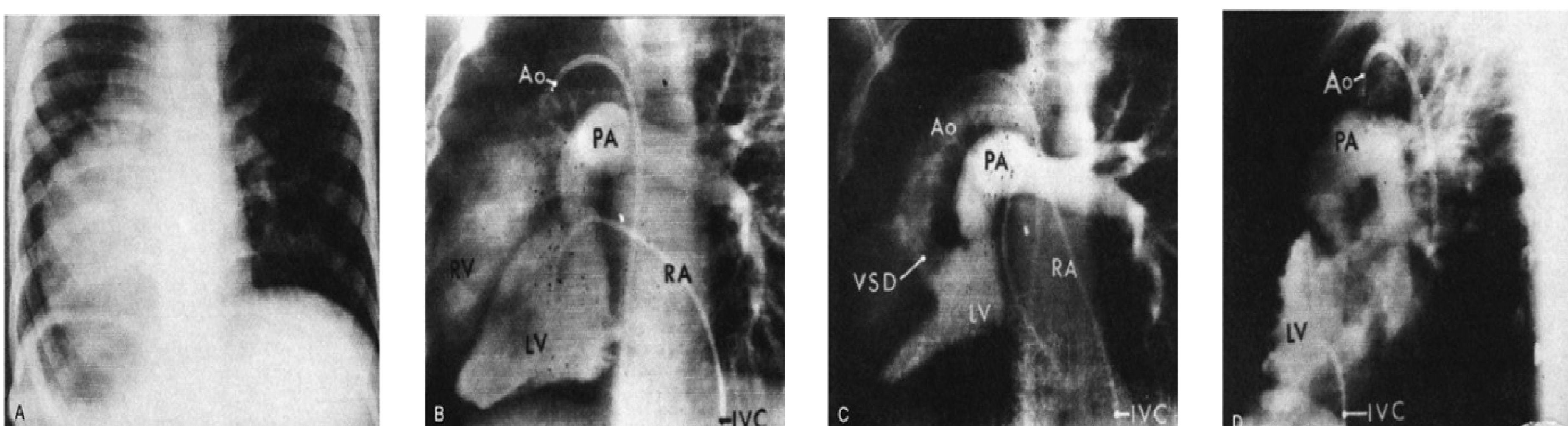
- CHD :
  - VSD
  - TOF
  - pulmonary atresia
  - complete AV septal defect
  - OS ASD.

Situs Inversus with Dextrocardia, Atrioventricular Concordance, and Ventriculoatrial Discordance with Left Anterior Aorta

- Inverted form of complete TGA
- The hemodynamics and physiology identical to TGA
- ECG :
  - inverted P-wave axis because of the atrial inversion
  - more evidence of associated right and left ventricular hypertrophy because of transposition physiology

Situs Inversus with Dextrocardia Atrioventricular and Ventriculoatrial Discordance, with Right Anterior Aorta

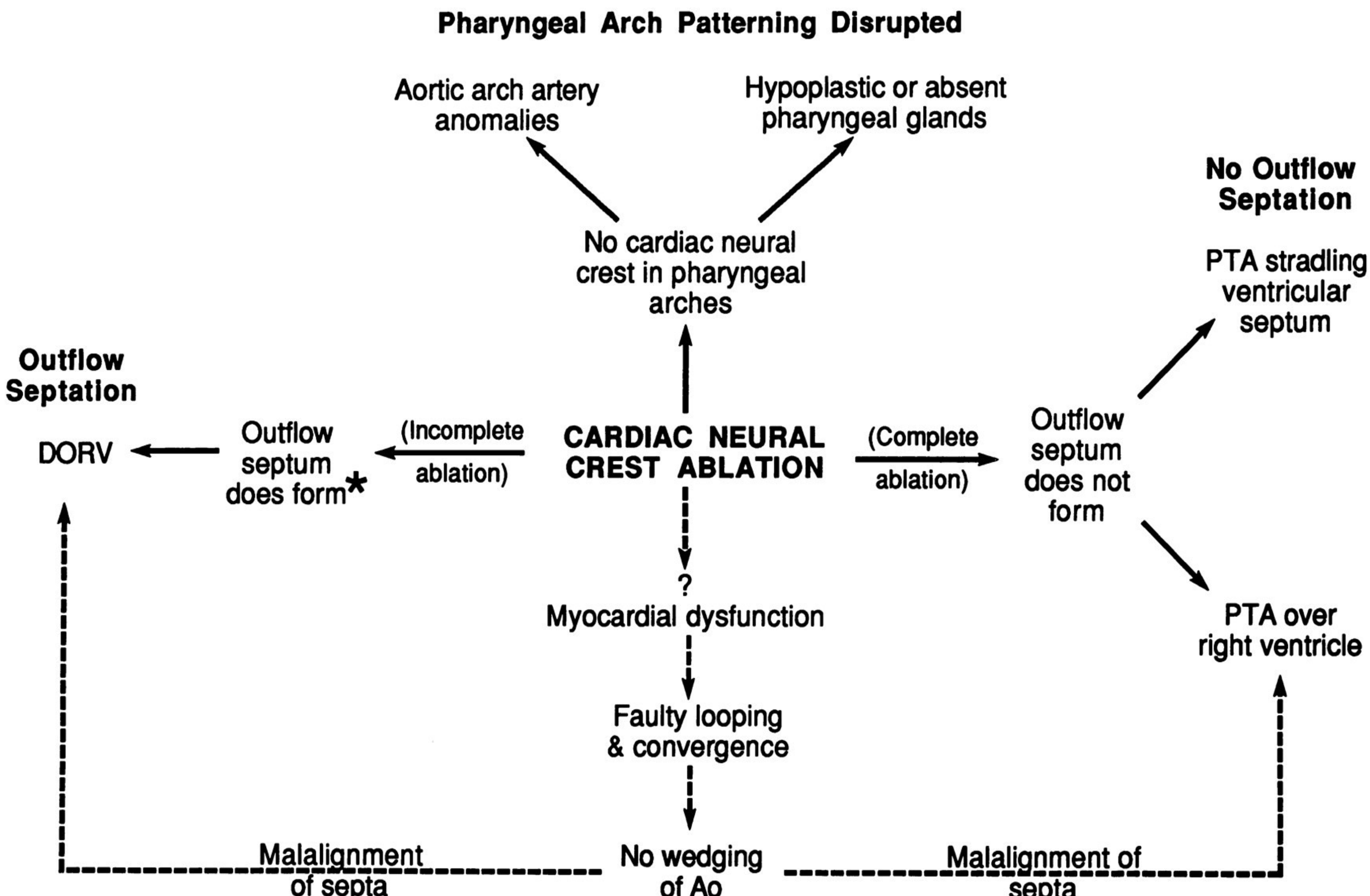
- Inverted form of corrected TGA
- Rare



Situs Inversus with Dextrocardia,

AV Discordance, and VA Concordance with Inverted NRGA

- Represents the inverted form of isolated ventricular inversion
- extremely rare
- cardiac abnormalities
  - common atrium
  - common AV valve
  - severe right ventricular hypoplasia.


Pharyngeal Arch Patterning Disrupted
Aortic arch artery anomalies
Hypoplastic or absent pharyngeal glands
No cardiac neural crest in pharyngeal arches
No Outflow Septation
PTA stradling ventricular septum
Outflow Septation
DORV
Outflow septum does form*
(Incomplete ablation)
CARDIAC NEURAL CREST ABLATION
(Complete ablation)
Outflow septum does not form
?
Myocardial dysfunction
PTA over right ventricle
Faulty looping & convergence
Malalignment of septa
No wedging of Ao
Malalignment of septa

MCQ'S

1.Coronary vessels develop from

- A. FHF
- B.SHF
- C.Neural Crest
- D.Proepicardium

- Answer D

2.All of the following are false except

- A.Right isomerism is associated with ectopic pacemaker
- B.Lungs are trilobed in left isomerism
- C.Complete heart block is presumptive evidence of right isomerism
- D.Interrupted IVC is seen in left isomerism
- Answer D

3.Intraembryonic blood vessels are seen on

- A. Day 18
- B.Day 19
- C.Day 20
- D.Day 22

- Answer C

4.All of the following are correctly matched except

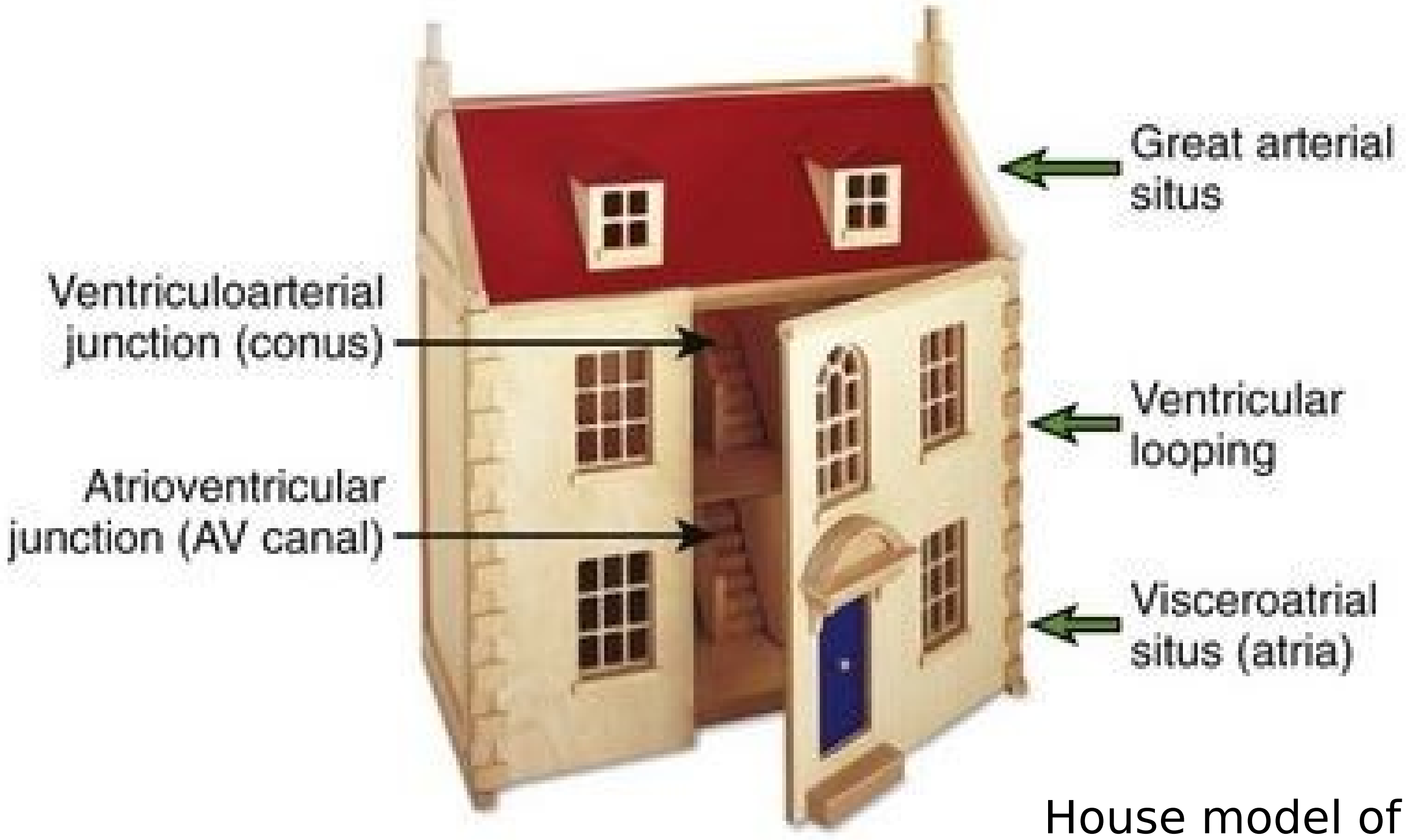
- A- NKX 2.5- Cardiac crescent induction
- B. eHand- RV myocyte
- C. TBX5- Septation
- D. GATA factors -Heart tube formation

- Answer B

5.Which of the following is false

- A.Mesocardia is always associated with congenital heart defects
- B.CCTGA-AV concordance with VA discordance
- C.Situs inversus with dextrocardia usually occurs with a structurally normal heart
- D.Right hemidiaphragm is lower in situs solitus with dextrocardia

THANK YOU



House model of HEART